

THE
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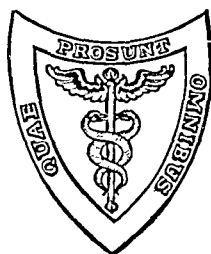
OF THE
MEDICAL SCIENCES

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NEW SERIES

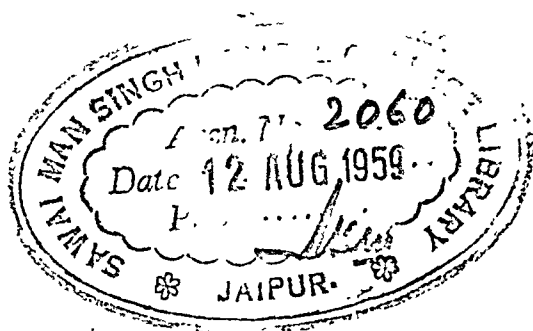
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THE
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JULY, 1939

ORIGINAL ARTICLES.

**ANTERIOR PITUITARY TUMOR ASSOCIATED WITH CACHEXIA,
HYPOGLYCEMIA, AND DUODENAL ULCER.**

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It is common to see symptoms referable to growth and development of the body and changes in the functional capacity of other endocrine organs in association with hypophyseal adenomas; in fact, diagnosis is frequently established on these findings alone even without local pressure phenomena. In the following case, a curious aggregation of symptoms was encountered in association with a tumor of the anterior lobe of the pituitary body, including persistent hypoglycemia, symptoms of cachexia hypophyseopriva, lowered metabolism, and a very active and incapacitating duodenal ulcer. So far as we have been able to ascertain, this particular combination has not previously been described, although each of the presenting symptoms has been noted separately in association with anterior hypophyseal lesions.

Case Report.—A man, a Jew, aged 28, registered at the clinic December 28, 1934, complaining of abdominal pain, vomiting, constipation and anorexia. His history was essentially negative. He had always been in good health and had been able to work steadily until the onset of this present illness a year before. His illness had begun with a sharp, periumbilical pain, occurring at first on 1 or 2 days a week, and later becoming fairly constant except for exacerbations which frequently occurred 3 to 4 hours after meals. He had never had a remission lasting more than a week. As the months progressed, the pain had become more severe and constant, awakening him frequently at night. At first, the distress had been partially relieved by food and soda. Probably because of dietary restrictions, constipation had also

developed and he had used laxatives and enemas freely. No melena or hematemesis had been noted at any time. He had been able to continue work for the first 8 months of his illness but, with the increasing severity of symptoms and subsequent loss of appetite and strength, he had been finally forced to give up his occupation as a laborer. His weight had dropped from 178 pounds to 140 (80.7 to 63.5 kg.), most of this loss having occurred in the 4 months prior to admission to the clinic.

Numerous physicians had been consulted concerning these complaints and the patient had been hospitalized in November, 1934, for complete roentgenologic examination of the gastro-intestinal tract; a dilated colon had been the only positive finding at the time. The patient had noticed no improvement on treatment directed at relief of the colonic stasis, but had become steadily worse and marked anorexia had developed. The smell and sight of food nauseated him; he vomited milk almost immediately after drinking it and the mere mention of food distressed him. There were a few articles of diet which he ate sparingly, but he had lived chiefly on fruit juices for 2 weeks preceding examination at the clinic and during this time vomited once or twice daily.

On examination at the clinic the patient appeared dull and lethargic; he was uncoöperative and unwilling to talk freely. He was 5 feet 9 inches in height (172.5 cm.) and weighed 140 pounds (63.5 kg.). There was evidence of recent loss of weight and the muscular tone was poor. The systolic blood pressure was 110, the diastolic 70. The pulse rate was 90 and the temperature 98.4° F. The general habitus was eunuchoid; his face was smooth and covered by a very fine hair. He shaved once a week. The skin was very dry and body hair was scanty and of the feminine type of distribution. The pupils reacted normally to light and accommodation; the ocular fundi appeared to be normal and the visual fields were negative. The lips were dry, cracked and of a thickened type; the tongue heavily coated; the tonsils were of medium size and cryptic, and there was a pungent, acidotic odor to the breath. The thyroid gland appeared to be normal in size. Examination of the thorax revealed prominent breasts; lungs and heart, normal. The abdomen was slightly distended, soft, and its walls had an unusually thick and doughy consistency. No masses could be palpated, but slight generalized tenderness was noted, more marked in the right upper quadrant. The genitalia were markedly underdeveloped and the prostate gland was smaller than normal. Inflamed hemorrhoids protruded. The deep and superficial reflexes were normal.

The patient was hospitalized on December 28, 1934, and laboratory examinations were carried out as his condition permitted. The value for hemoglobin was 12.15 gm. per 100 cc. of blood; erythrocytes numbered 4,820,000 and leukocytes 8600 per c.mm. A differential count was essentially normal. Serologic tests for syphilis were negative. The urine had specific gravity of 1.025; it was acid and contained albumin graded 2, no sugar, hyaline casts (graded 2) and an occasional pus cell per microscopic field. Subsequent urinalyses were negative.

Venous blood (1 hour after the noon meal on day of admission) contained: urea 20 mg., sugar 43 mg. and chlorides 487 mg. per 100 cc.; the carbon dioxide combining power was 80.5 volumes %. Intravenous infusion of 1 liter of 10% glucose and 1% saline solution was given immediately on receiving these reports and this procedure was repeated daily for 8 days thereafter. The fasting value for blood sugar on the following morning was found to be 60 mg. %; another fasting value was obtained Jan. 2 and was reported as 44 mg. Blood chlorides were 611 mg. %, and carbon dioxide combining power of the plasma was 67.3 volumes % on this date.

The patient was carefully watched and closely questioned regarding symptoms of hypoglycemia, but no evidence of any untoward reaction or

sensation could be elicited. He neither showed nor could recall any symptoms that are commonly noted in spontaneous hypoglycemia or with insulin reactions. Fasting and delay in getting his meals, even when he was working, had never caused him to become weak; he had never noted any excessive sweating, diplopia, attacks of weakness, convulsions, or related conditions. Frequent estimations of blood sugar and chlorides were made during the patient's 31-day stay in the hospital (Table 1). The highest reading for blood sugar obtained at any time was 78 mg. %, the lowest 30 mg. (Jan. 17). These levels were not affected by a high intake of carbohydrate or by intravenous infusions of glucose. The patient vomited glucose solution given by mouth so that the glucose tolerance could not be satisfactorily determined.

TABLE 1.—DETERMINATIONS OF BLOOD SUGAR, CHLORIDES, AND CARBON DIOXIDE COMBINING POWER.

Date.	Time.	Blood sugar, mg. per 100 cc.	Blood chlorides, mg. per 100 cc.	Carbon dioxide combining power volumes %.		
1934.						
12-28	1.30 P.M.	43	487	80.5	1 liter 10% glucose and 1% salt, intravenously	One hour after noon meal.
12-29	8.30 A.M.	60	1 liter 10% glucose and 1% salt, intravenously, daily from Dec. 29 to Jan. 4	Fasting.
1935.						
1- 2	8.30 A.M.	44	611	67.3		Fasting.
1- 4	Noon	1 cc. ant. pit. extract, intramusc.	
1- 5	8.30 A.M.	40	676	60.7	...	Fasting.
	10.30 A.M.	49				
1- 8	8.30 A.M.	43	544	Fasting.
1- 9	10.30 A.M.	38	561	Fasting.
1-11	4.30 P.M.	45	511	..	Operation; transfusion; 500 cc. 20% glucose intravenously, cortin, 10 cc.	After breakfast.
1-12	8.30 A.M.	65	544	..	500 cc. 20% glucose; cortin, 10 cc. daily	After breakfast.
	9.30 P.M.	52	479			
1-13	8.30 A.M.	65	553	..	Cortin, 10 cc. daily	After breakfast.
1-14	8.30 A.M.	38	561	..	Cortin, 10 cc. daily	After breakfast.
1-15	8.30 A.M.	33	528	After breakfast.
1-17	8.30 A.M.	30	536	..	Cortin, 10 cc. daily	After breakfast.
1-18	8.30 A.M.	66	503	After breakfast.
1-19	8.30 A.M.	60	528	After breakfast.
1-20	8.30 A.M.	59	528	After breakfast.
1-23	8.30 A.M.	38	561	Fasting.
1-25	8.30 A.M.	52	Fasting.

In view of the peculiar and unexplained hypoglycemic state and the eunuchoid habitus, the possibility of some pituitary disturbance was at once suspected. A Roentgenogram of the head revealed enlargement of the sella turcica, grade 4, with thinning of the posterior clinoid processes (Fig. 1). Following this report, the visual fields were examined by accurate

perimetric methods and a bitemporal hemianopia for small objects and for color was demonstrated. Specific questioning regarding possible symptoms from this presumably extensive chiasmal lesion gave negative results. The patient could not recall any noticeable visual disturbances, headache, dizziness, or other symptoms which could be attributed to increased intracranial pressure. The vomiting, which was a prominent symptom, had never been of the projectile type.

Two determinations were made of the basal metabolic rate; the first (performed on Dec. 29, 1934) was -23% , and the second (performed on Jan. 5, 1935) was -22% . The blood cholesterol, on Jan. 5, was 175 mg., the blood lecithin 248 mg. The total volume of plasma was 49 cc. per kilo, the total blood volume 72.8 cc. per kilo. The blood calcium and phosphorus readings were found to be 11.6 and 1.3 mg. % respectively. An analysis of the gastric content following the intramuscular injection of histamine was made on Jan. 5, 1935, and repeated on Jan. 9 using epinephrine as a stimulant. The results are shown in Table 2. It is interesting that larger volumes of secretion and even higher values for gastric acidity were obtained following the administration of epinephrine.

TABLE 2.—RESULTS OF ANALYSIS OF GASTRIC CONTENTS.

Specimen.	January 5.		
	Amount, cc.	Free HCl, units.	Total acid, units.
1	20	24	54
2	35	66	80
6.7 mg. histamine injected intramuscularly			
3	40	84	98
4			
5	50	80	92
6	35	90	100
7	45	110	120
8	20	114	122
<hr/>			
Total secretion in 80 minutes, cc.	245		
Specimen.	January 9.		
	Amount, cc.	Free HCl, units.	Total acid, units.
1	120	86	100
1	30	100	112
3	30	76	86
4	20	86	92
9 minims epinephrine hydrochloride injected intramuscularly			
5	75	104	114
6	50	110	118
7	50	110	124
8	45	132	138
<hr/>			
Total secretion in 80 minutes, cc.	420		

* Roentgenologic examination of the stomach revealed a duodenal ulcer. This was regarded as the probable explanation of the patient's abdominal pain and subsequent experience with ulcer therapy confirmed this opinion. Roentgenologic examination of the colon was reported as giving negative results, although the organ appeared to be rather large and atonic.

It seemed necessary that the pituitary tumor should receive attention first, particularly since it was beginning to cause defects in the visual fields and since it was also considered to be primarily responsible for the patient's hypoglycemia and cachexia; however, the multiplicity of abnormal changes which this patient presented made evident the added risk that would attend



FIG. 1.—Enlargement of sella turcica with thinning of posterior clinoid processes.

an operation of this type. For this reason, further laboratory and therapeutic measures were carried out with the hope that some means might be discovered to raise the blood sugar to a higher, and possibly a safer, level for the operative procedure or to counteract any crisis that might occur postoperatively. Anterior pituitary extract was used, with negative results; the effect of epinephrine was also studied (Table 3). While epinephrine produced a temporary increase in the value for blood sugar, suprarenal cortical hormone had no effect on the patient's general condition or on the value for blood sugar, as will be noted later.

TABLE 3.—EFFECTS OF EPINEPHRINE ON THE BLOOD SUGAR.

Time, A.M.				Blood pressure.		Blood sugar, mg. per 100 cc.
				Systolic.	Diastolic.	
10.30	9 minims	epinephrine	injected	120	68	38
			subcutaneously		at 10.30	
10.35	.	.	.	136	70	
10.45	55
10.50	.	.	.	130	70	
10.55	62
11.00	.	.	.	122	66	
11.03	62

The final preoperative diagnosis was pituitary adenoma, with involvement of the optic chiasm, secondary hypoglycemia, eunuchoidism and duodenal ulcer. On the 15th day after admission, right transfrontal craniotomy was done for the removal of the pituitary tumor and a large, cystic, degenerating pituitary adenoma was exposed. The tumor was shaped like a mushroom (Fig. 2), the stem rising between the optic nerves. The dome-like portion was cystic and had compressed the third ventricle; the base rested on the optic chiasm. The cyst was emptied of about 10 cc. of yellow fluid. Only a portion of the tumor was removed as it seemed to infiltrate the adjacent structures and, because of its vascularity, it seemed better to treat it postoperatively with radiotherapy. A transfusion of 500 cc. of blood was given during the course of the operation. Microscopically, the tumor proved to be a chromophobe adenoma.

There was surprisingly little reaction to the operation and the patient's convalescence was relatively uneventful; by 8 P.M. on the day of operation he was asking questions and was able to move all his extremities. His axillary temperature rose to 100.3° F. the day following the operation, after which it remained normal.

The patient was watched closely for any symptoms of hypoglycemia or other symptoms following operation, but none appeared. Estimations of blood sugar and chlorides were made every 6 or 8 hours postoperatively during the first 2 days and daily thereafter. Intravenous injections of 5 cc. of suprarenal cortical hormone, as prepared by Kendall, were given in the evening of the first and second days following operation. Following this he received from 5 to 20 cc. of the suprarenal cortical hormone intramuscularly for 3 days. This was without apparent effect on the patient's general condition or on the value for blood sugar.

Sweetened fruit juices and a diet high in carbohydrate were given on the second day after operation, and this was tolerated fairly well until the fifth day, when the patient began to vomit. He was then placed on a bland ulcer diet and remained comfortable; no alkalies or sedatives were necessary to control the digestive symptoms. The patient was transferred to the Radiologic Section on Jan. 21, 1935, and received high voltage therapy for 5 days over the lower frontal, occipital, right and left temporal, and vertex regions of the head. He had considerable reaction from these treatments, became quite nauseated, and vomited several times.

Neurologic and ophthalmoscopic examinations were made just prior to the patient's final dismissal, on Jan. 25, 1935, but the results were no different from those obtained before operation. At the time of dismissal his general condition was good. The partial removal of the pituitary tumor and Roentgen therapy of the pituitary area did not have any apparent effect in restoring the blood sugar to a normal value. The patient died about 2 months following dismissal. Details of his final illness were not obtained, death presumably occurring from exhaustion and cachexia.

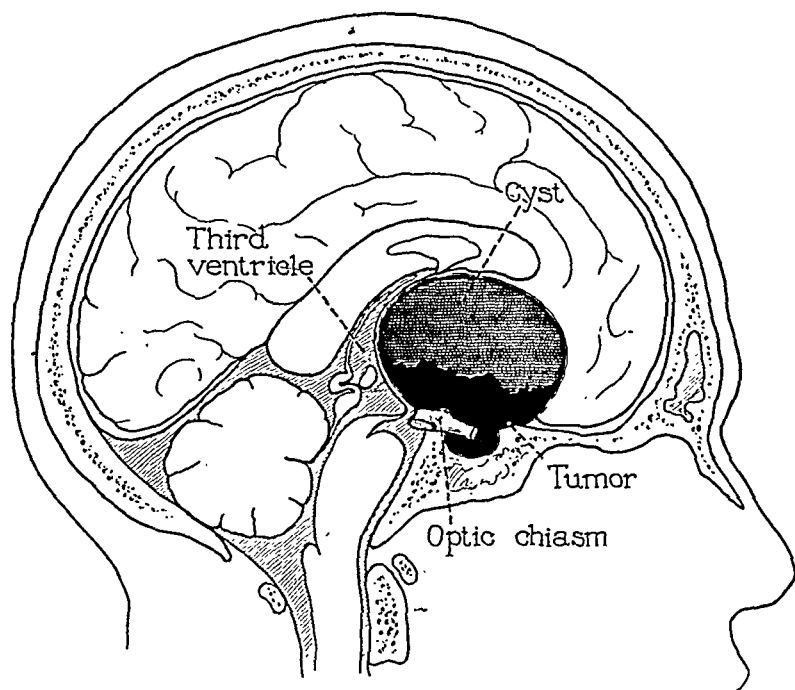


FIG. 2.—Situation of tumor and its relationship to hypophysis and third ventricle.

In reviewing this case it seems probable that all of the patient's symptoms were secondary to the presence of the original neoplasm, which undoubtedly arose from the anterior lobe of the hypophysis. It is further believed that these symptoms were in general referable to the destruction of the anterior lobe and suppression of its hormonal activity. The lethargy, depression, and general decline in health were thought to be due to the general depressing effects of loss of anterior lobe secretions on tissue metabolism; the genital atrophy and the abnormalities of the secondary sexual characteristics were thought to be due to the loss of the gonadotropic hormone and the chronic hypoglycemic state was thought to be due to the loss of the diabetogenic hormone. The low basal metabolic rate may have been due in part to malnutrition and inactivity, or it may be explained on the basis of failure of the anterior lobe to provide the proper stimulus for thyroid function. The duodenal ulcer, which produced symptoms of unusual severity, is comparable to the peptic ulcers which follow lesions of the third ventricle.

Brain Lesions and Their Relation to Peptic Ulcer. Rokitsansky (1841-1846) appears to have been the first to regard ulcerative processes of the gastro-intestinal tract as being of neurogenic origin. Since then several other investigators have reported cases of gastric and duodenal ulceration associated with intracranial lesions.^{1,2,8,11,14,21} Cushing (1932),^{5b} in an excellent review of the subject both from the clinical and experimental aspects, again aroused interest in the occurrence of gastric and duodenal ulceration associated with lesions of the brain. Comroe⁴ (1933) reported 2 cases of pituitary tumor associated with peptic ulcer, and Swan and Stephenson¹⁹ have recently reported a case of basophilic adenoma of the pituitary in which death occurred after hemorrhage from a large penetrating gastric ulcer.

One may summarize the whole matter by stating that there is both clinical and experimental evidence to suggest that intracranial lesions may produce changes in the gastro-intestinal tract, and that these changes may take the form of both acute and chronic peptic ulceration. In the case reported herein there can be little doubt that the hypophyseal neoplasm antedated the formation of the duodenal ulcer, but the etiologic importance of the former in the production of ulcer can only be surmised.

Hypoglycemia of Hypophyseal Origin. The occurrence of hypoglycemia in the case herein reported was perhaps the most striking single clinical feature. The extremely low values for blood sugar, with the absence of symptoms referable to such a condition, the lack of response to high carbohydrate diets and to intravenous infusions of glucose and epinephrine, and the persistence of the low value for blood sugar, even after removal of a portion of the tumor, are particularly worthy of comment. We were unable to find the report of a single case in the literature on pituitary tumor associated with a value for blood sugar as low as 0.30 mg. % in the absence of hypoglycemic symptoms.

Cushing (1912)⁵ was probably the first to report a proved case of hypoglycemia associated with pituitary tumor. Wilder (1930)²⁰ reported 2 cases in which there were neuropsychiatric symptoms and a periodic loss of consciousness associated with the periods of hypoglycemia. Enlargement of the sella turcica was demonstrated in both of these cases and one patient had the appearance of being mildly acromegalic. Discussing the relation of pituitary lesions to hypoglycemia, Wilder cited cases of this type previously reported by Frazier,⁷ Jacob,¹⁰ Pribram,¹⁵ Stenström¹⁸ and Meng.¹³ There has been much experimental evidence in support of the theory that the pituitary gland plays a part in carbohydrate metabolism. The reader is referred to the excellent reviews of this subject by Houssay,⁹ Long,¹² Russell¹⁷ and Colwell.³ Kepler and one of us⁶ (M. P. F.) are studying the relation of glucose tolerance curves to pituitary tumors; the results of this study will be reported in a subsequent publication.

Studies of blood sugar and glucose tolerance tests unfortunately could not be carried out in our case long after operation and Roentgen therapy; however, the association of an anterior hypophyseal lesion, cachexia, and a persistent and severe but asymptomatic hypoglycemia adds another example to the series collected by Wilder. The mechanisms involved are obscure and the best explanation at present available is that there may be some interference with the relations between the diabetogenic hormone of the anterior hypophysis and insulin.

Relation of Hypophyseal Lesions to Basal Metabolism. The low metabolic rate in our case has been mentioned previously and needs no additional comment, since the finding of a low rate is a very common accompaniment of hypophyseal lesions and one which has been discussed frequently. Such lowered states of metabolism are particularly common in pituitary cachexia, such as this patient presented; they may represent, in such instances, not only an endocrine effect, but secondary changes in nutrition.

Summary. The presenting symptoms of a patient with a large cystic chromophobe adenoma of the anterior hypophysis were those of penetrating duodenal ulcer. Such a lesion was demonstrated roentgenologically and symptomatic relief was obtained on ulcer management. The patient also had definite hypoglycemia; the level of the blood sugar was not permanently elevated by a high carbohydrate diet, intravenous infusions of glucose, suprarenal cortical hormone, or anterior pituitary extracts. Epinephrine produced a slight temporary increase. The blood sugar was not affected by removal of a portion of the tumor and subsequent radiotherapy. Cachexia, eunuchoidism, and lowered metabolism were additional features. The probable relation of these symptoms to the original hypophyseal lesion is discussed.

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MINERAL APPETITE OF PARATHYROIDECTOMIZED RATS.*

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BIOCHEMICAL studies have demonstrated the existence of marked disturbances in the mineral metabolism of parathyroidectomized animals. It has been shown that the serum calcium falls to a very low level and that the accompanying tetany and other deficiency symptoms may be eliminated by the administration of calcium (MacCallum and Voegtlin;⁷ Lieberman and Szurek⁴). Evidently, parathyroidectomized animals have an increased calcium need.

In a previous study, it was reported that, given free, but not forced access to calcium lactate solution (2.4%), parathyroidectomized rats ingested large quantities and thereby seemed to make an effort to satisfy their increased calcium need (Richter and Eckert⁸). Of the 18 rats tested, 17 drank an average of 3.9 times more calcium lactate solution after parathyroidectomy than before. Parathyroid implants made to the anterior chamber of the eyes quickly reduced the calcium lactate intake to its normal level.

Although it seemed very likely from these experiments that parathyroidectomized rats have a calcium craving, a definite conclusion to this effect could not be drawn without showing that the rats have an increased appetite for other calcium solutions besides the lactate. The first part of the following experiments deals with the appetite of parathyroidectomized rats for calcium gluconate, calcium acetate, and calcium nitrate.

Biochemical studies have also shown that removal of the parathyroids results in a marked phosphorus retention (Greenwald and Gross;³ Greenwald;² Weaver and Reed;¹² Esau and Stoland¹). Phosphate administered in the diet in large amounts increases tetany (Salvesen, Hastings and McIntosh⁹). Experiments were performed to determine whether this phosphorus retention has any effect on phosphate appetite, whether the parathyroidectomized rats exhibit a phosphate aversion or craving.

For some time it has been known that parathyroid tetany improves under treatment with strontium and magnesium salts (Luckhardt, Waud and Brannon;⁶ Swingle and Wenner¹¹). Experiments were undertaken, therefore, to determine whether parathyroidectomy increases the appetite for strontium and magnesium.

* These experiments were supported by grants from the Rockefeller Foundation and from the Committee for Research in Endocrinology of the National Research Council.

Methods. The animals were kept separately in cages, $7\frac{3}{4}$ by $12\frac{1}{2}$ by 10 inches, containing a food cup and, in most of the experiments, only 2 inverted 100 cc. graduated bottles. One bottle contained tap water, the other a calcium, strontium, magnesium or phosphate solution. Daily records of the fluid intake were made for several weeks before operation and for at least 40 days afterwards. Rats on the calcium and phosphate choices received the standard McCollum diet but minus the 1.5% calcium carbonate; rats on the strontium and magnesium choices received the standard McCollum diet with the calcium carbonate. Rats on the multiple choice of mineral solutions received a low mineral diet, kindly furnished us by Dr. W. B. Cox of the Mead Johnson Laboratories.

The operative technique requires no detailed comment beyond the statement that an effort was made not to rupture the parathyroid capsule nor severely injure the thyroid. Only one pair of parathyroid glands was found in each animal.

The following solutions were used in these experiments:

	Per cent.		Per cent.
Calcium lactate	2.4	Sodium lactate	4.0
Calcium gluconate	0.3	Potassium chloride	2.0
Calcium nitrate	0.5	Strontium chloride	0.02
Calcium chloride	1.0	Strontium lactate	0.02
Calcium acetate	0.01	Magnesium chloride	0.5
Sodium phosphate (dibasic) . .	4.0	Magnesium lactate	0.02

The selection of the concentration of the solutions depended on the following considerations: the solutions had to be strong enough to permit the rat to distinguish them easily from tap water and yet not so strong that the rats refused them entirely. A previous paper contains the details of the process used to determine these concentrations (Richter and Eckert,⁸). The apparent preference of the rats for solutions of these concentrations remains unexplained.

Results. Appetite for Calcium. It was found that parathyroidectomized rats have an increased appetite for solutions of calcium gluconate, nitrate, and acetate as well as lactate. Figure 1 shows the records of 3 typical animals. The calcium gluconate intake of the first animal increased from a level of approximately 10 cc. per day before parathyroidectomy to a level near 28 cc. 20 days after. The calcium nitrate intake of the second animal increased from a level near 5 cc. per day to a peak of 29 cc. 39 days after parathyroidectomy. The calcium acetate intake of the third animal increased approximately the same amount.

Table 1 summarizes the results. It includes also data obtained from 27 animals on a calcium lactate choice. All except one of these 27 rats showed an increased calcium lactate intake. The average daily intake for the group increased from 4.6 cc. for the 10-day period immediately preceding parathyroidectomy to 17.7 cc. during the 20 to 30-day postoperative period. The ratio of the increase was 3.84.

Three rats on a calcium acetate choice showed an increased intake. The average daily intake increased from 3.6 cc. to 11.2 cc., giving a ratio of 3.11. Three out of 4 rats showed a markedly increased

calcium gluconate intake. Three rats on calcium nitrate choice showed a smaller but definitely increased intake.

TABLE 1.—CALCIUM (SINGLE CHOICE).

McCollum food without calcium carbonate.

Solution.	No. of animals.	Number showing.			Average daily intake in cc.		Average ratio 20-30 days after: 10 days before.
		Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20-30 days after parathyroidectomy.	
Calcium lactate, 2.4% .	27	26	1	0	4.6	17.7	3.84
Calcium acetate, 0.01% .	3	3	0	0	3.6	11.2	3.11
Calcium gluconate, 0.3% .	4	3	1	0	7.1	10.4	1.46
Calcium nitrate, 0.5% .	3	3	0	0	3.8	4.9	1.29

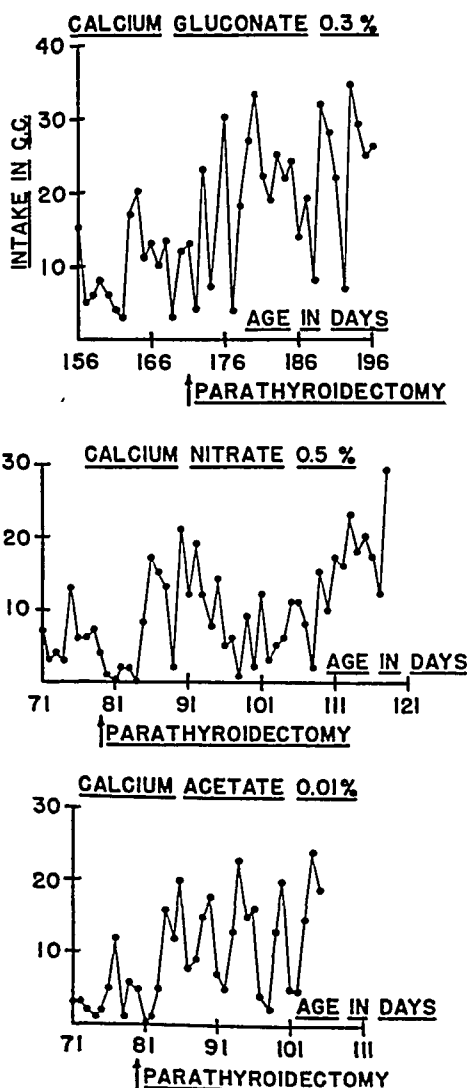


FIG. 1.—Records of 3 typical animals showing daily intake of various calcium salts before and after parathyroidectomy.

These experiments show that parathyroidectomized rats have an increased calcium craving.

Appetite for Phosphate. In the first part of these experiments 6 rats were each given access to 3 bottles, containing tap water, calcium lactate, 2.4% solution, and dibasic sodium phosphate, 4% solution, respectively.

After parathyroidectomy the rats drank more of the calcium lactate and less of the dibasic sodium phosphate solution. Table 2A summarizes the results. Five of the 6 rats showed an increased calcium lactate intake, giving a ratio of 2.63. Five out of 6 decreased their dibasic sodium phosphate intake, giving a ratio of 0.43.

In the second part of the phosphate experiment, 6 rats fed a low mineral diet (Cox) each had access to 6 bottles containing tap water, calcium lactate, dibasic sodium phosphate, calcium chloride, potassium chloride, and sodium lactate, respectively. Figure 2 presents a typical record of one animal showing the daily intake of each of these solutions for 17 days before parathyroidectomy and for 43 days afterwards. The calcium lactate intake increased from a level of 1 to 2 cc. per day before parathyroidectomy to a level of 30 cc. 40 days later. The increase occurred almost at once after parathyroidectomy, reaching 18 cc. on the second day. In sharp contrast the dibasic sodium phosphate intake decreased from an average level of 7 cc. to a level of 3 cc. Sodium lactate intake also decreased, while the intake of calcium chloride and potassium chloride remained unchanged.

TABLE 2A.—CALCIUM AND PHOSPHATE CHOICE.

Full McCollum Diet (6 Animals).

Solution.	Number showing.			Average daily intake in cc.		Average ratio 20-30 days after:10 days before.
	Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20-30 days after parathyroidectomy.	
Calcium lactate, 2.4%	5	0	1	4.9	12.9	2.63
Sodium phosphate, 4% (dibasic)	0	1	5	6.8	2.9	0.43
Water	1	0	5	33.0	26.1	0.79

TABLE 2B.—MULTIPLE MINERAL CHOICE.

Cox's Low-mineral Diet (6 Animals).

Calcium lactate, 2.4%	5	1	0	7.3	21.9	3.0
Potassium chloride, 2%	3	2	1	1.4	1.0	0.75
Sodium lactate, 4%	2	0	4	3.0	3.0	1.0
Calcium chloride, 2%	1	5	0	0.5	0.5	1.0
Sodium phosphate, 4% (dibasic)	0	0	6	5.5	1.9	0.35
Water	0	1	5	22.3	10.0	0.45

Table 2B summarizes the results for 6 rats. The average daily intake of calcium lactate increased from 7.3 cc. for the 10-day period preceding parathyroidectomy to 21.9 cc. for the 20 to 30-day post-

operative period, giving a ratio of 3.0 which is almost the same as that obtained in the calcium experiments described above. At the same time, the average daily dibasic sodium phosphate intake decreased from 5.5 cc. to 1.9 cc., giving a ratio of 0.35. The average daily intake of potassium chloride, calcium chloride, and sodium lactate remained practically unchanged.

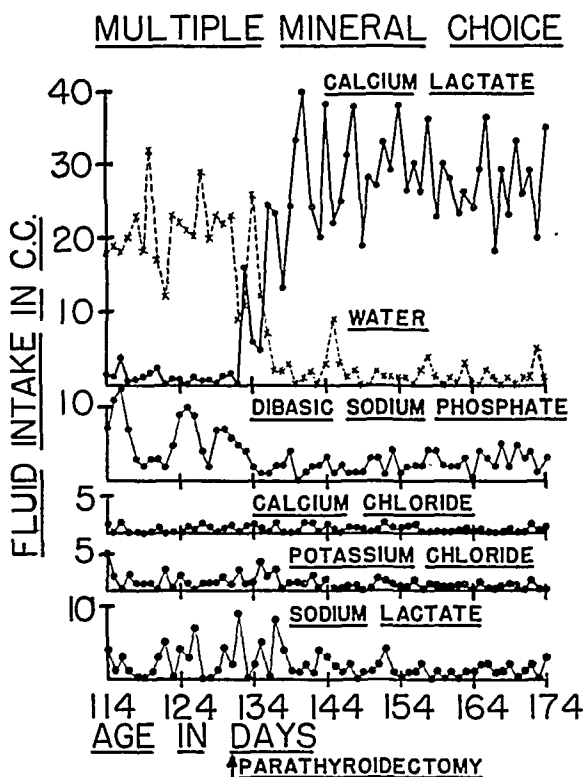


FIG. 2.—Record of a typical animal showing daily intake of 5 salts and water before and after parathyroidectomy.

These experiments show that a phosphate aversion apparently accompanied the calcium craving.

Appetite for Strontium and Magnesium. It was found that the parathyrectomized rats have an increased appetite also for strontium and magnesium solutions. Figure 3 shows 2 typical records. The first record presents the intake curves for water and strontium chloride for 18 days before parathyroidectomy and 42 days afterwards. During the 18-day period the daily intakes of water and the strontium solution were nearly the same, averaging 18 to 20 cc. On the fourth day after parathyroidectomy the intake of strontium chloride increased sharply to 36 cc. while the water intake decreased to 4 cc. Parathyroid implants made to the anterior chamber of the eyes 25 days after parathyroidectomy caused the strontium chloride

intake to decrease and the water intake to increase sharply within 8 days. The magnesium chloride intake of the other animal increased from an average daily intake of 5 cc. before parathyroidectomy to a level near 40 cc. 30 days afterwards.

Table 3 summarizes the results. Three out of 4 rats showed an increased strontium chloride intake. The average daily intake increased from 8.2 cc. for the 10 days preceding parathyroidectomy to 17.2 cc. in the 20 to 30-day period afterwards, giving a ratio of 2.10. The magnesium chloride intake showed a similar increase. The increase in the intake of the strontium lactate and magnesium lactate solutions was less marked.

TABLE 3.—OTHER MINERALS (SINGLE CHOICE).

Full McCollum Diet.

Solution.	No. of animals.	Number showing.			Average daily intake in cc.		Average ratio 20-30 days after: 10 days before.
		Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20-30 days after parathyroidectomy.	
Strontium chloride, 0.02%	4	3	1	0	8.2	17.2	2.10
Strontium lactate, 0.02%	3	2	1	0	7.1	8.8	1.24
Magnesium chloride, 0.5%	3	3	0	0	11.2	23.1	2.06
Magnesium lactate, 0.02%	4	1	3*	..	2.7	3.9	1.44

* All died of tetany within 24 hours.

The results show that parathyroidectomized rats apparently have an increased appetite for strontium and magnesium as well as for calcium.

Discussion. These experiments indicate that, given an opportunity, parathyroidectomized rats, like adrenalectomized rats, make mineral selections which are conducive to the maintenance of a normal physiological equilibrium. Adrenalectomized rats, given a saltless diet and without access to any salt solution, suffered 100% mortality, dying after an average of 9 days. When the rats were given access to a salt solution, the mortality decreased sharply and most of the animals continued to grow at the normal rate. Given access to several mineral solutions containing most of the essential electrolytes, the mortality decreased to zero, and all rats showed normal growth. Obviously the rats made beneficial selections.

Parathyroidectomized rats, kept on a low calcium diet (McCollum diet without calcium carbonate) and without access to calcium, showed a 52% mortality. Thirteen out of 25 rats died, in most instances within the first 24 hours. All of the surviving rats showed tetany for at least 10 days and lost weight for 10 to 20 days. However, given access to calcium solutions (lactate, acetate, gluconate, and nitrate), parathyroidectomized rats made selections which reduced the mortality to zero, greatly reduced the tetany, and either eliminated or reduced the weight loss.

The parathyroidectomized rats clearly indicated an increased appetite for calcium, especially for calcium lactate. It has been reported that calcium lactate is more efficient in relieving symptoms of tetany in animals and humans than any other calcium salt given orally, provided it is given with water (Luckhardt and Goldberg⁵, Wilson¹³).

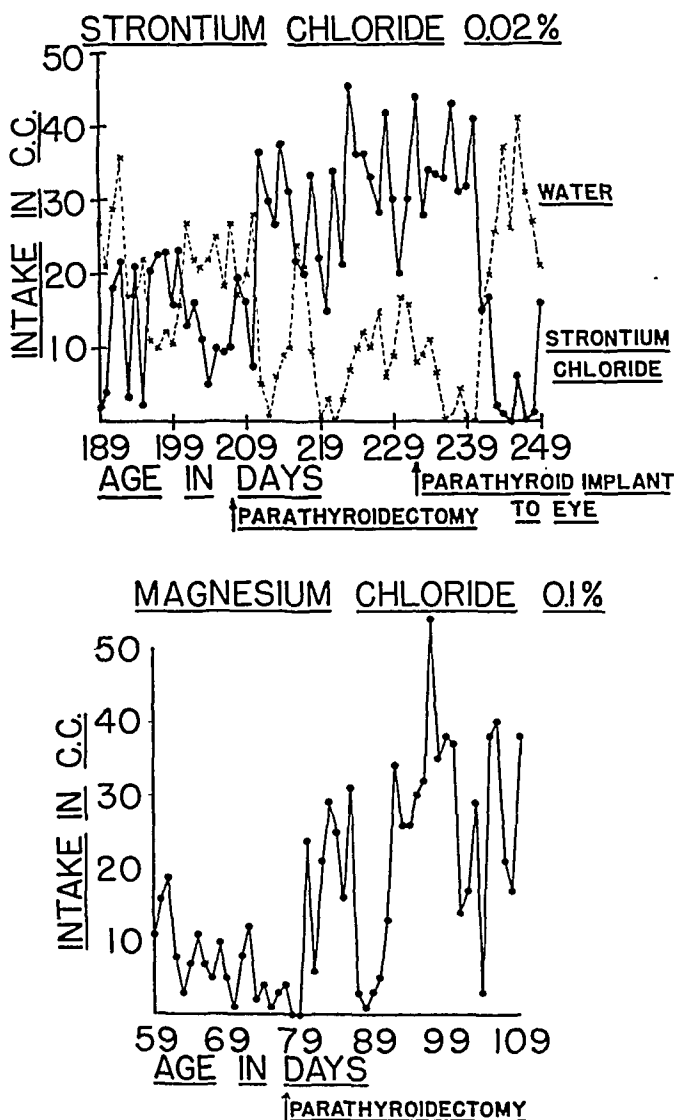


FIG. 3.—Records of 2 typical animals showing daily intake of strontium chloride and magnesium chloride before and after parathyroidectomy.

The increased appetite for strontium and magnesium is of special interest because of the close atomic relation of these two elements to calcium.

It is even possible that parathyroidectomized rats may have an

increased appetite for other minerals. Numerous single and multiple choice experiments made with sodium and potassium solutions, however, did not reveal cravings for these minerals.

The aversion for phosphate has already been described by Shelling.¹⁰ He states that parathyroidectomized rats will display an appetite for diets rich in calcium and low in phosphorus, but will refuse to partake of diets low in calcium or high in phosphorus. Moreover, it appears that a high phosphate diet is refused only when the phosphate is in a form that the animal can use, and hence retain. Diets in which the phosphate is in an unusable form (the meta-form) are not refused. Evidently the phosphate retention plays an important rôle in the appetite of parathyroidectomized animals. The present study confirms these findings. The craving for calcium and the aversion toward phosphate are no doubt results of the decreased serum calcium and the phosphate retention.

At the present time, it would appear that the selections made by the rats may depend, not on a trial and error process, but on chemical changes in the taste mechanisms in the oral cavity, making the calcium more desirable after parathyroidectomy than before. The craving for calcium may almost be considered as a tropism response. Section of the taste nerves should give an answer to this question.

Summary. 1. Parathyroidectomized rats showed a markedly increased appetite for calcium solutions (lactate, acetate, gluconate, and nitrate) and an aversion toward dibasic sodium phosphate solution.

2. Parathyroidectomized rats also showed an increased appetite for strontium and magnesium salt solutions.

3. These results agree with the present knowledge concerning the disturbed calcium and phosphorus metabolism after parathyroidectomy.

4. The decreased mortality and alleviation of deficiency symptoms of parathyroidectomized rats given access to calcium solutions add further proof that rats have an ability to make selections conducive to their well-being.

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ADRENAL APOPLEXY IN A MAN OF 72 FOLLOWING IDIOPATHIC THROMBOPHLEBITIS OF THE ADRENAL VEINS.

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MASSIVE bilateral hemorrhage into the adrenal glands is uncommon, and in adults extremely rare. Less than a dozen cases above the age of 20 years have been recorded and thus far none over the age of 55. A number of very complete reviews and discussions of the syndrome associated with massive adrenal hemorrhage has appeared recently^{1,3,5-8,11}. The purpose of the present communication is to record the clinical picture and post-mortem findings in a man who developed this syndrome at the age of 72.

Case Report.—M. F. (BIH 19213), male, entered the hospital on May 14, 1934, complaining of excruciating upper abdominal pain of 24 hours' duration. His family history was negative. Past history revealed pneumonia and typhoid fever 50 years previously. About 2 years before admission he developed a slightly productive cough and 10 months before admission had a few small hemoptyses. He was seen in the Out-patient Department where a diagnosis of carcinoma of the lung was established. He received no treatment for this condition. In the 2 years preceding admission he had also been troubled by chronic constipation and bleeding piles. On May 14, 1934, at about noon the patient was suddenly seized with a severe stabbing pain in the midline above the umbilicus. He vomited 4 or 5 times during the next few hours, the vomitus consisting of mucus and clear colorless fluid. The pain persisted until the time of admission in spite of the subcutaneous injection of morphia by his local physician.

Physical examination revealed a poorly nourished old man writhing in pain. The right chest was dull anteriorly in its upper portion and breath sounds were diminished over this area. A few fine râles were heard over this area also, and numerous crackling râles were audible at the bases. The abdomen was board-like, with exquisite tenderness and rebound tenderness above the umbilicus. The temperature was 98.8° by rectum, pulse 104, respirations 32, and blood pressure 140 mm. of mercury systolic and 95 mm. of mercury diastolic. The white blood cell count was 20,000 per c.mm.

A diagnosis of ruptured hollow viscus was made and the patient taken to the operating room immediately. Under local anesthesia supplemented with gas oxygen and ether the abdomen was opened. Careful exploration revealed no abnormality of any sort within the peritoneal cavity and the abdomen was closed. After operation the patient's blood pressure was 110 mm. of mercury systolic and 60 mm. of mercury diastolic. These soon fell to 70 and 50 respectively. The patient rapidly failed in spite of supportive treatment, developing air hunger and cyanosis. He died 10 hours after operation.

Autopsy (A-34-61, Drs. Fienberg and Frehling). The adrenal glands were swollen and, particularly in and about the medulla, markedly hemorrhagic. There was also considerable hemorrhage into the capsules of both glands.

The other gross findings included a neoplastic nodular mass infiltrating

almost all of the right upper lobe of the lung, and extending into the mediastinum where it impinged on and invaded the wall of the superior vena cava and the right subclavian vein. These vessels contained small non-occluding thrombi over the invading tumor tissue. The coronary arteries and aorta showed a slight amount of arteriosclerosis. A few tiny patches of extravasated blood were found in the gastric mucosa and the renal pelvis. No other thrombosed veins were found anywhere. Blood culture was negative.

Microscopic examination of the adrenal glands showed the large and small veins to be occluded by recent ante-mortem thrombi. The walls of these vessels showed moderate to marked edema and acute inflammatory cell reaction. There was marked hemorrhage into the medulla and surrounding tissue entirely obliterating the normal histology. The cells of the cortex in many areas were completely necrotic; in others, marked vacuolization of the cytoplasm and pyknosis of the nuclei were predominant. There was acute inflammatory cell infiltration within the gland and also external to the capsule. The arteries and arterioles were free of thrombi.

The rest of the microscopic examination confirmed the gross findings and revealed in addition scattered fibrotic patches in the kidneys, and slight necrotic changes and fibrin deposit in the splenic corpuscles.

Discussion.—Massive bilateral adrenal hemorrhage occurs in a variety of diseases. It has been noted in the neonatal period, in septicemias of various sorts, usually meningococcic or pneumococcic, in fatal diphtheria, following trauma, in severe burns, in purpura, and in thrombophlebitis of the adrenal veins of unknown etiology.^{1,3,5-8,11} Most of the cases recorded in the literature have occurred in children with fulminating septicemia. The symptoms associated with the syndrome depend to a considerable degree on the underlying pathologic process. Thus when a septicemia is responsible for the process the patients exhibit severe purpura, high fever and signs of meningitis, in addition to the signs and symptoms due to the adrenal hemorrhages themselves and the syndrome is called the Waterhouse-Friderichson Syndrome.^{1,6,8} In this syndrome, the massive bilateral adrenal hemorrhages are usually not associated with venous thrombosis but are due to arterial or capillary embolization. In adults, pain is frequently the presenting symptom. The pain may occur over the costovertebral angles, or, as in the case recorded here, over the upper abdomen. In the case described in this paper, the abdominal pain was excruciating and was accompanied by board-like rigidity of the abdominal wall. The diagnosis of perforated abdominal viscus was not confirmed by exploratory laparotomy and subsequent autopsy. The cases of Barsoum² and of Hall and Hemken⁵ were also subjected to laparotomy because of the nature and distribution of the pain. In adults, the underlying cause is usually thrombophlebitis of the adrenal veins of unknown etiology. In occasional instances the patient may have peripheral thrombophlebitis as in the case reported by Pearl and Brunn.⁷ In all cases, no matter what the etiology, shock, usually rapidly progressive, is a prominent manifestation and is the cause of death. The occurrence of shock following the sudden destruction of both

adrenal glands is to be expected from what is known of the physiology of those organs.

The factor responsible for the development of the adrenal vein thrombophlebitis in the case here reported, as in other cases in the literature, is unknown. No connection between the thrombophlebitis and the carcinoma of the lung could be established. This type of case is best regarded as one of that group of instances of visceral thrombophlebitis of unknown etiology which may also localize in the portal vein,¹⁰ inferior vena cava,⁴ hepatic veins,⁹ renal veins,⁴ or mesenteric veins,¹² each giving rise to a typical symptom complex depending on the organs involved.

Summary.—A case of idiopathic thrombophlebitis of the adrenal veins with bilateral adrenal apoplexy occurring in a man of 72, suffering from carcinoma of the lung is reported. The clinical picture of this syndrome is discussed. It is pointed out that this condition falls into the group of syndromes due to visceral thrombophlebitis which may involve the veins of any abdominal viscus, giving rise to a variety of signs and symptoms depending on the organ involved.

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REPORT OF 50 CASES OF ACUTE LOBAR PNEUMONIA IN ADULTS TREATED WITH SULPHAPYRIDINE.

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IN the Henry Ford Hospital over the preceding 8 years 678 cases of lobar pneumonia have been treated by all methods, both with and without serum. Of these, 253 have died (37%). These patients were all adults, with no exceptions made on the basis of day of disease, type of pneumococcus or condition on admission.

During the past winter 50* unselected, consecutive adult cases of

* Since the above report was prepared, 20 additional cases of lobar pneumonia in adults have been treated with sulphapyridine. There were 2 deaths. The mortality for the entire 70 cases was therefore 8.5%.

lobar pneumonia were treated with sulphapyridine. In this series there were 4 deaths, a mortality of 8%. Only those patients who presented history and physical findings considered typical of lobar pneumonia were included in this series, and all had from one to several chest Roentgen ray examinations. Blood cultures were made in all cases.

TABLE 1.—PNEUMOCOCCUS TYPING OF PNEUMONIA CASES TREATED WITH SULPHAPYRIDINE.

Type.	No. of cases.
I	4
II	5
III	5
IV	5
V	2
VII	10
VIII	2
XVIII	1
	<hr/> 34

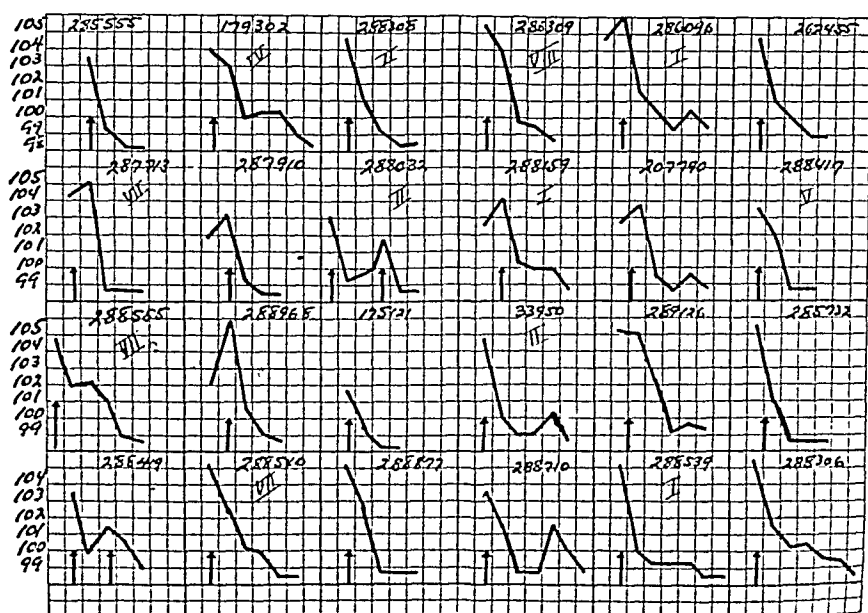


FIG. 1.—Maximum temperature. Arrow indicates beginning of sulphapyridine in 24 cases. Each space = 1 day.

No pneumococcus typing could be determined by our methods in 15 of the cases. In this series only 5 patients received anti-pneumococcus serum. All patients received sulphapyridine. The exhibition of sulphapyridine did not vary materially. Routinely, after the clinical diagnosis was established and sputum and blood cultures obtained, an initial dose of 3 gm. of the drug was given, followed in 2 hours by 2 gm. and then 1 gm., every 4 hours until a total of from 15 to 25 gm. had been administered, or until the temperature reaction was favorable.

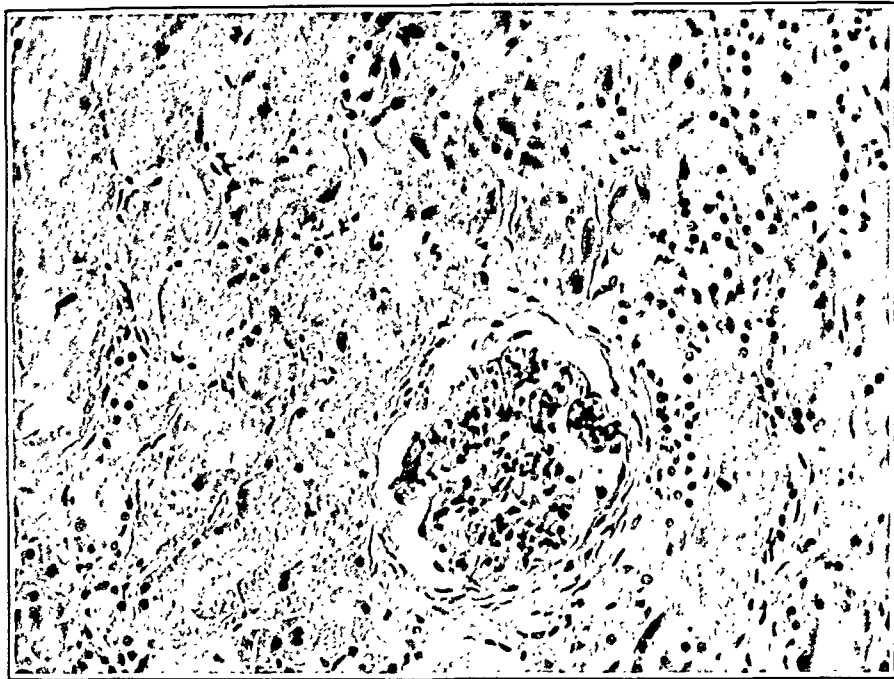


FIG. 2.—Case 1. Kidney (medium power), showing tubular necrosis in localized area about glomerulus. Tubular epithelium stains uniform pink and is desquamating.

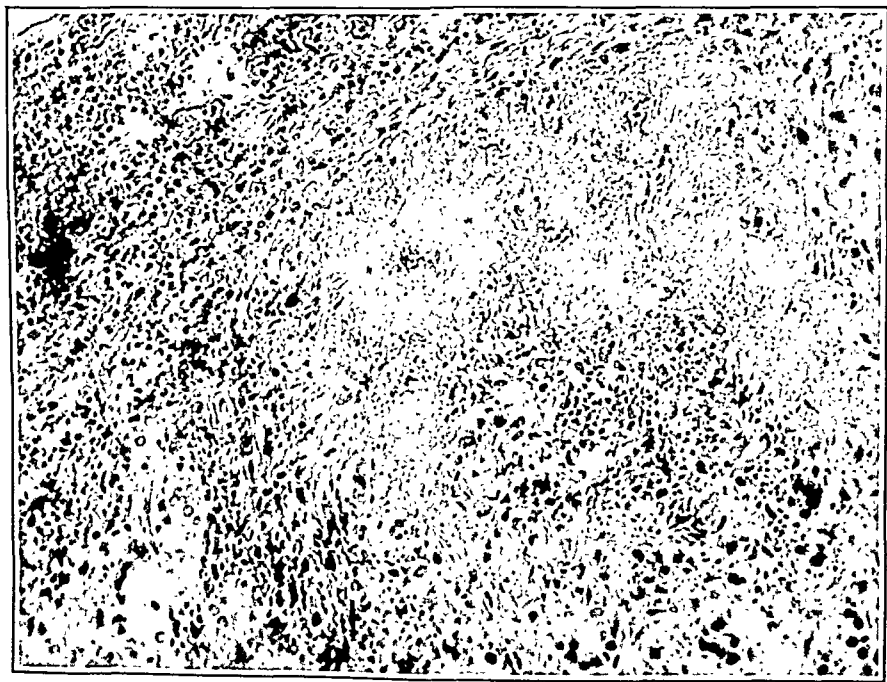


FIG. 3.—Case 1. Adrenal (medium power), showing areas of necrosis in cortex surrounded by areas of hemorrhage.

The common temperature response to the drug is exemplified by the accompanying chart of 24 sulphapyridine-treated cases. Prompt and abrupt defervescence was the rule; and failure to develop this typical response led to the justified suspicion that a non-pneumococcic infection might be the causative agent in 3 cases. Two of these at autopsy proved to be instances of staphylococcus pneumonia, and 1 a tuberculous pneumonia.

Only 1 pneumococcus complication occurred, an instance of empyema—the patient making a recovery with intercostal drainage.

As with other investigators, we found nausea to be the common reaction of practically all patients treated with the drug. This was in many instances severe, but in no case did its presence prevent the use of the drug.

In many instances, large jagged arrowhead-shaped crystals of sulphapyridine were found in the urine toward the end of the drug therapy, but no evidence of renal damage was encountered save in 1 instance (Case 1).

No effect was seen on the blood picture. Cyanosis was not thought to be present in our cases in any greater degree than in any other similar group of lobar pneumonias treated by other methods.

Four deaths occurred as follows:

CASE 1.—G. G. white female, aged 54. Semicomatose 8th day of disease. Type III pneumococcus (sputum). Right lower lobe involved. Urine showed 3+ albumin and occasional red cell. After 8 gm. of the drug had been administered, developed anuria and treatment was stopped. Temperature had fallen with treatment and remained at low level several days. Renal function returned in 2 days but a new consolidation developed and death occurred without further specific treatment.

Autopsy (Dr. Frank Hartman) showed a resolving pneumonia of the right lower lobe and a fresh consolidation of the left upper lobe. The kidneys showed acute toxic nephritis with both tubular degeneration and focal necroses. Focal necroses were also present in the adrenals.

CASE 2.—I. D., white male, aged 76. Sputum and blood culture showed Type II pneumococcus. Treated with serum with marked thermal reaction and then both serum and sulphapyridine. Death on the 9th day.

CASE 3.—F. P., white male, aged 64. Admitted 3d day. Sputum and blood both positive for Type IV pneumococcus. Showed satisfactory temperature response but after 18 hours of normal temperature developed ventricular tachycardia (E. K. G.) and died during this attack.

CASE 4.—M. B., white male, aged 51. Admitted 7th day. Sputum and blood both positive for Type VII pneumococcus. Also had syphilis, was a chronic alcoholic and was in auricular fibrillation with a ventricular rate of 160. Died 18 hours after admission.

Summary. To add to the existing records of the sulphapyridine treatment of acute lobar pneumonia in adults, 50 unselected consecutive cases so treated are presented with a mortality of 8% contrasted with a previous mortality in a series of 678 cases of 37%.

Aside from nausea, only one toxic effect was encountered thought due to the drug—an instance of acute toxic nephritis and focal necrosis in the adrenal, confirmed by autopsy.

THE RESULTS OF SULFAPYRIDINE THERAPY IN 400 CASES OF TYPED PNEUMOCOCCIC PNEUMONIA.*

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In previous reports^{7,8} we have reviewed the earlier experimental and clinical data pertaining to the use of sulfapyridine in pneumococcal infection; in the second of these,⁸ we reported our clinical experience with sulfapyridine therapy in 100 cases of pneumococcic pneumonia. These 100 cases are included in the 400 cases reported in this paper. Since their publication, confirmatory experimental work in the laboratory and clinical results with this drug have been reported from widely separated sources.^{1-3,5,9,11,16,18} In the main, the mortality, toxic reactions, and complications in our clinical studies have been the same as in other clinics. The purpose of this paper is twofold, to report the results of 400 typed cases† of pneumonia treated in Philadelphia with sulfapyridine, and to present certain observations made while using the drug. We have studied 100 additional cases in which no typable pneumococcus could be obtained, but have not included data on these cases in this analysis of dosage, therapeutic results, influence of the drug on the course of the disease, complications, and toxic effects. In these patients, the diagnosis of pneumonia was definitely established by clinical and laboratory studies. Roentgen examinations were made in 66% of the cases and blood cultures were taken in 94%, although some of the cultures were not taken until after treatment had been started. All but 7 of the patients were followed personally by the authors.

We have included in this report every patient who received treatment for 12 hours or more. Seven patients are excluded who

* Merck & Co., of Rahway, N. J., kindly supplied the Sulfapyridine used in this study.

† Most of our cases were seen at the following hospitals in and around Philadelphia: Philadelphia General, Hospital of the University of Pennsylvania, Hahnemann, Graduate, Misericordia, Presbyterian, Episcopal, Mt. Sinai, Fitzgerald-Mercy, St. Mary's and Germantown.

died in less than 12 hours after drug therapy was begun. Sulfapyridine therapy was instituted in every patient with pneumonia offered to us for study from whom a typable pneumococcus was recovered, regardless of complications or the apparent severity of the infection. Patients who received therapeutic doses of serum either before or after sulfapyridine therapy are not included in this report. Even though we tried to avoid a combination of the two types of therapy, 12 patients were given both serum and sulfapyridine. One death occurred in the group of 5 that had sulfapyridine followed by serum and one in the other group of 7 that received serum first.

TABLE 1.—RESULTS OF SULFAPYRIDINE TREATMENT IN 400 TYPED CASES.

Type.	Negative blood culture.			Positive blood cultures.			Total.		
	No. of cases.	Fatal cases.	Mortality, %.	No. of cases.	Fatal cases.	Mortality, %.	No. of cases.	Fatal cases.	Mortality, %.
I	83	3	3.6	21	3	14.3	104	6	5.8
II	27	1	3.7	3	1	33.3	30	2	6.7
III	63	10	15.9	4	1	25.0	67	11	16.4
IV	20	1	5.0	2	1	50.0	22	2	9.1
V	31	0	..	6	2	33.3	37	2	5.4
VI	13	0	..	0	0	..	13	0	
VII	21	1	4.8	0	0	..	21	1	4.8
VIII	23	0	..	1	0	..	24	0	
IX	4	0	..	0	0	..	4	0	
X	1	0	..	0	0	..	1	0	
XII	8	0	..	0	0	..	8	0	
XIII	1	0	..	0	0	..	1	0	
XIV	17	0	..	1	0	..	18	0	
XV	4	1	25.0	1	0	..	5	1	20.0
XVI	3	0	..	1	1	100.0	4	1	25.0
XVII	2	0	..	0	0	..	2	0	
XVIII	4	0	..	0	0	..	4	0	
XIX	7	0	..	0	0	..	7	0	
XX	2	0	..	0	0	..	2	0	
XXI	1	0	..	0	0	..	1	0	
XXII	2	0	..	0	0	..	2	0	
XXIII	6	0	..	0	0	..	6	0	
XXIV	2	0	..	0	0	..	2	0	
XXV	3	1	33.3	0	0	..	3	1	33.3
XXVII	4	0	..	0	0	..	4	0	
XXVIII	2	1	50.0	0	0	..	2	1	50.0
XXIX	3	0	..	1	0	..	4	0	
XXX	1	0	..	0	0	..	1	0	
XXXI	1	0	..	0	0	..	1	0	
Total .	359	19	5.3	41	9	22.0	400	28	7.0

Therapeutic Results. The results of the sulfapyridine treatment are given in Table 1; 84% of the cases were caused by the pneumococcus Types I to VIII and Type XIV. In 197 cases, approximately one-half of the entire group, the pneumococcus involved belonged

to one of the first three types. In this group of 197 cases, the mortality was 9.6%. There were 104 cases of Type I infection with a mortality of 5.8% and 63 cases of Type III infection with a mortality of 16.4%. The mortality rate of Type III is generally high, due we believe to the fact that the Type III organism is often the cause of pneumonia in debilitated or senile patients. This is suggested by the average age of 54.6 years in the group of 11 fatal cases of

TABLE 2.—ANALYSIS OF FATAL CASES IN TYPED SERIES.

Number.	Age, years.	Day of disease treatment began.	Type.	Total dosage, gm.	Remarks.
1	44	6	I	8	Moribund on admission
2	43	8	I	50	Developed empyema and meningitis
3	63	5	I	8	Moribund on admission
4	56	3	I	8	Moribund on admission
5	58	3	I	21	Cardiac decompensation
6	55	1	I	30	Temp. nor.; died of coronary occlusion
7	73	1	II	24	
8	57	3	II	12	Moribund on admission
9	35	7	III	6	Moribund on admission
10	75	3	III	32	
11	51	5	III	10	Moribund on admission
12	65	4	III	5	Moribund on admission
13	66	2	III	35	
14	58	14	III	25	Severe alcoholic
15	47	14	III	20	Pneumonia complicating subac. bact. endocarditis
16	57	10	III	25	Uremic on admission
17	68	6	III	19	Cardiac decompensation
18	79	3	III	25	Chr. card. decomp.
19	45	7	III	19	Moribund on admission
20	62	5	IV	11	Moribund on admission
21	70	6	IV	9	Card. decomp. on adm.
22	57	8	V	10	
23	12	4	VII	20	Clinically well. Died in epileptic convulsion
24	32	5	VII	102	Developed empyema and meningitis
25	57	4	XV	25	Cardiac decompensation
26	37	3	XVI	5	Paretic. Moribund on admission
27	68	2	XXV	35	
28	37	7	XXVIII	25	Temp. nor. Diabetic. Died in insulin shock

Type III infection. The incidence of bacteremia in this series was low. In only 41 patients was a positive blood culture obtained, with a mortality in this group of 22%. An analysis of all the fatal cases is presented in Table 2. Every patient receiving treatment for more than 12 hours who died during the period of hospitalization has been counted as a death from pneumonia. This has resulted in the inclusion of 4 cases as deaths in which the patients had fully recovered from the pulmonary infection. Case VI died on the fifth

day of convalescence of coronary occlusion; Case XXIII died in a epileptic convulsion just before discharge; Case XXV, a chronic cardiac died after 10 days of normal temperature in a sudden attack of decompensation; Case XXVIII died in a hypoglycemic reaction following insulin on the fifth day of normal temperature. The mortality in both the white males and females was higher than in either sex in the negro (Table 3). The incidence and mortality according to age are given in Table 4. In Table 5 we have attempted to show the influence of pre-existing disease or complicating conditions on mortality. In those pneumonia patients who had had pre-existing nephritis or cardiac disease the mortality (23.7%) was approximately 3 to 4 times the mean mortality for the typed group as a whole.

TABLE 3.—INCIDENCE AND MORTALITY ACCORDING TO RACE AND SEX IN TYPED SERIES.

Race.	Sex.	No. of cases.	Incidence, %.	No. of deaths.	Mortality, %.
White . . .	Male	190	47.5	15	8.0
	Female	113	28.3	9	7.9
Negro . . .	Male	63	15.7	3	4.8
	Female	34	8.5	1	2.9

TABLE 4.—INCIDENCE AND MORTALITY AMONG AGE GROUPS IN TYPED SERIES.

Age groups.	No. of cases.	Incidence, %.	No. of deaths.	Mortality, %.
12 to 19	45	11.2	1	2.2
20 to 29	71	17.8	0	
30 to 39	74	18.5	4	5.4
40 to 49	86	21.5	4	4.7
50 to 59	59	14.8	9	15.3
60 to 69	42	10.5	6	14.3
70 and over	23	5.8	4	17.4

TABLE 5.—INFLUENCE OF OTHER DISEASES ON MORTALITY IN TYPED CASES.

Disease.	No. of cases.	Fatal cases.	Mortality, %.
Heart disease	28	7	25.0
Syphilis	20	1	5.0
Diabetes	15	1	6.7
Postoperative	13	0	
Nephritis	10	2	20.0
Alcoholism	8	1	12.5
Asthma	8	0	
Pregnancy	8	0	
Cirrhosis	2	0	

Dosage. The majority of the patients were treated according to the dose schedule recommended by Evans and Gaisford.⁶ An initial dose, by mouth, of 2 gm. was followed by 1 gm. every 4 hours until a total of 25 gm. had been given. Our experience has led us to modify the total dosage in certain respects. Though patients treated during the first 5 days of their disease received, as a rule, a total of 25 gm., when therapy was begun more than 5 days after the onset, a total of 15 gm. was usually sufficient to con-

trol the infection. Every patient with a positive blood culture received at least 25 gm.; in a few instances a total of 50 gm. was given. Whenever there was evidence of spread of the infection, even though the temperature had dropped to normal, larger total amounts were administered. The level of sulfapyridine in the blood was estimated at least once during the course of treatment in the majority of the patients. As stated in our former paper,⁸ we have not been able to correlate concentration of the drug in the blood with either the dose or the clinical result. The average level of sulfapyridine in the blood was between 4 and 6 mg. per 100 cc. (range from 1.2 to 18 mg.).

In elderly patients and especially those with renal involvement the total dosage rarely exceeded 15 gm. The possibility that in this group there was impaired elimination of the drug was suggested by a high level of sulfapyridine in the blood of several patients after relatively small doses of the drug. On the other hand, one patient, who developed a typical Type V pneumococcic pneumonia during an acute nephritis, had a low level of sulfapyridine in the blood after 7 gm. of the drug had been given within 24 hours.

This man, aged 47, had had gross hematuria, a cloud of albumin, and a low fixed specific gravity for 2 weeks before developing pneumonia. He was given the routine treatment of sulfapyridine, consisting of an initial dose of 2 gm. followed by 1 gm. every 4 hours. After 6 doses, or a total of 7 gm. had been given without the development of vomiting, his blood level of sulfapyridine was only 3.8 mg. per 100 cc. of blood. On the same day the level of urea nitrogen in his blood was 120 mg. per 100 cc. of blood. In spite of this low level of sulfapyridine in the blood and the azotemia, there was a critical fall in temperature on the day after treatment was started. It is of interest that with recovery from the pneumonia, there was rapid improvement in the nephritis, so that after 5 days of sulfapyridine therapy repeated urinalyses showed no red blood cells and only a faint trace of albumin. The level of blood urea nitrogen improved steadily to be 29 mg. per 100 cc. 17 days after the course of sulfapyridine was started.

The question of renal damage by sulfapyridine is becoming increasingly more important. Stockinger²⁰ first reported finding sulfapyridine crystals in the urine of treated patients. Antopol and Robinson⁴ and Gross, Cooper and Lewis^{10a,b} have found urinary concretions composed mainly of free and acetylated sulfapyridine in rats, rabbits and monkeys given sulfapyridine orally. More recently, Southworth and Cooke¹⁹ have reported hematuria, abdominal pain and nitrogen retention in 3 patients who had been given sulfapyridine by mouth.

Our data were analyzed with a view to discovering renal damage. Of 381 patients who had urinalyses during the acute stage of the disease, red blood cells were found in the urine of 27 cases, a hematuria incidence of 7%. As Reimann^{17a} states that casts and red blood cells are found in about 4% of lobar pneumonia cases, it would appear that hematuria was significantly increased in our

patients after sulfapyridine therapy. In only 14 of 277 patients who had urinalyses during treatment, however, was hematuria discovered after the initiation of sulfapyridine therapy. This incidence of 5.4% is but little above Reimann's hematuria incidence.

In most cases hematuria was observed in but one or two specimens and often disappeared even though sulfapyridine medication was continued. The following case is representative of this group.

A male, aged 18, with a Type V pneumonia, was treated on the third day of his disease with sulfapyridine. On the fifth day, the urine was found to contain many red cells and abundant albumin. A careful search of the sediment did not reveal any crystals of the drug. On the next day, the red cells were less numerous, and on the seventh day despite the fact that the sulfapyridine medication had not been stopped, the urine was clear. There was no increase in the blood urea nitrogen and during convalescence a urea clearance of 120% of average normal function was reported. Dr. Eugene Landis in consultation believed that in this patient the hematuria and albuminuria were due, not to the sulfapyridine but to a focal nephritis such as may occur in an acute febrile illness.

In a further attempt to discover any harmful effect of sulfapyridine therapy on the kidney, sections of kidneys from 12 fatal cases were examined by Dr. Herbert Fox. He observed no consistent change from normal that could not be explained by an acute febrile illness.

In spite of our failure to demonstrate renal damage, the high incidence of hematuria, which in 3 cases was gross, and the laboratory and clinical experience of others leads us to believe that renal damage during sulfapyridine treatment may be regarded in the future as one of the more common sequelæ of this type of drug therapy.

At this time we cannot state definitely what constitutes adequate dosage. It is well recognized from comparisons of dosage and blood concentration that there is a wide variation in the rate of absorption in different patients, and in the same patient from day to day. It is quite probable that establishment of optimum blood concentration of the drug must await more soluble derivatives of sulfapyridine, and more extensive studies on the acetylated and non-acetylated drug. At present, we are not in a position to state what constitutes the optimum blood level of the drug. The fact that we have observed excellent clinical improvement in patients whose blood level did not exceed 2.0 mg. per 100 cc. indicates the limitations of simple blood level determinations.

Influence of the Drug on the Course of the Disease. The most striking clinical observation was the frequency and rapidity of the drop in temperature after the drug treatment was started. This drop in temperature, which usually occurred within 24 to 36 hours, was in most instances followed closely by definite improvement in the toxemia and general well-being of the patient. The critical

termination of the febrile course after therapy was begun, even in the first few days of the disease, was very dramatic as can be seen in Charts 1 and 2.

Whether or not resolution of the pneumonic consolidation is hastened by the action of the drug, we have been unable to determine. The fact that physical signs often persisted for some days after the temperature had become normal, the toxemia had disap-

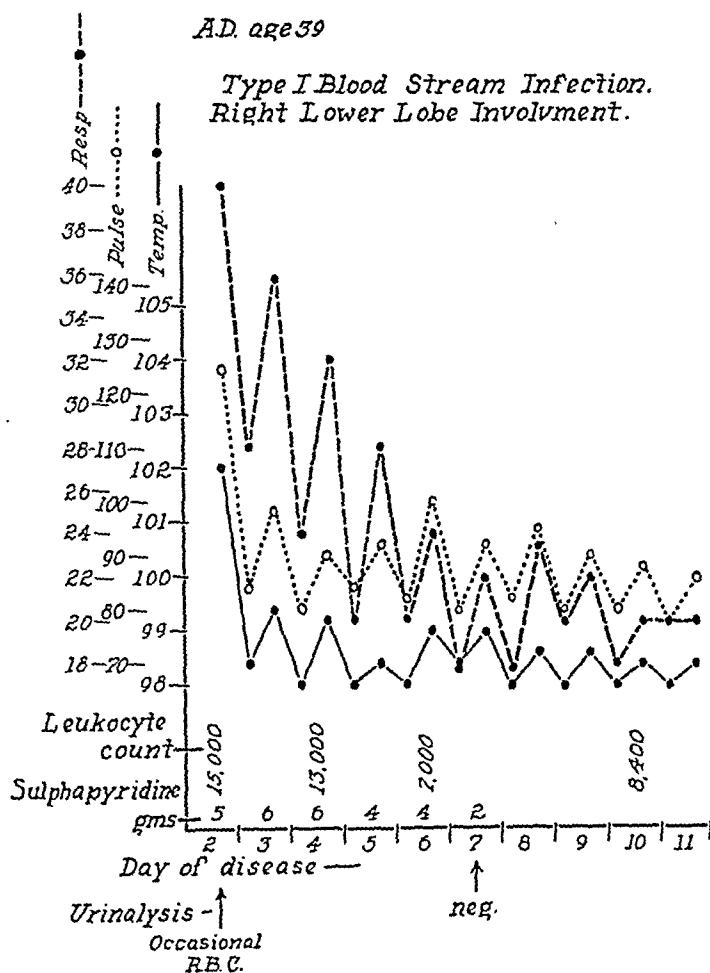


CHART 1.

peared, and the general well-being of the patient had returned to normal, strongly suggests that once red hepatization has occurred the pathologic changes in the lung must undergo their usual process of resolution even though bacterial invasion is no longer a problem. In a few patients, however, who gave a typical history of the onset of pneumococcal pneumonia (chill, bloody sputum and chest pain), therapy was started before true pulmonary consolidation could

be demonstrated by either physical or Roentgen examination. In these cases, followed by frequent Roentgen and physical examinations, dense consolidation seemed to be aborted and resolution of the process to occur more readily.

The relationship between the day of disease on which therapy was started and the drop in temperature is given in Chart 3. In the majority of patients the temperature fell by crisis. In some, a low grade fever persisted for several days after the critical drop; in

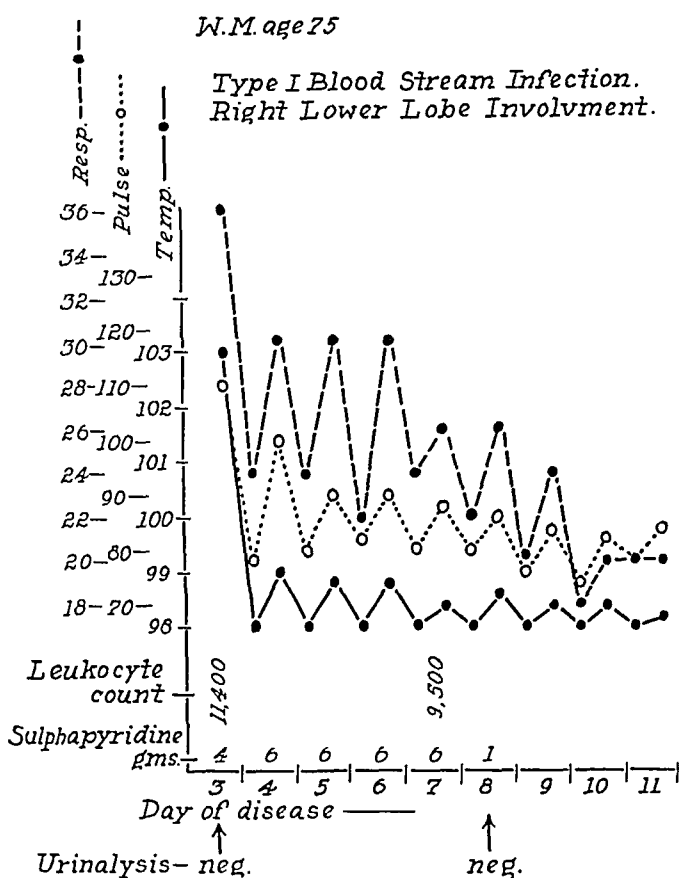


CHART 2.

such cases careful evaluation of the individual factors was required before outlining further therapy. Blood counts and urinalyses were obtained as frequently as possible within reason during the course of treatment and convalescent period. Even though the cases were followed personally by one of the authors, the fact that they were drawn from more than 15 hospitals, including a large municipal hospital, made regular studies almost impossible. In most patients, the critical drop in temperature was followed within 12 to 24 hours by a rapid fall toward normal of the total white blood count. This,

we believe, represents a favorable sign, because in cases in which the leukocyte count remained elevated, despite what was thought to be adequate drug therapy, the usual clinical improvement was retarded.

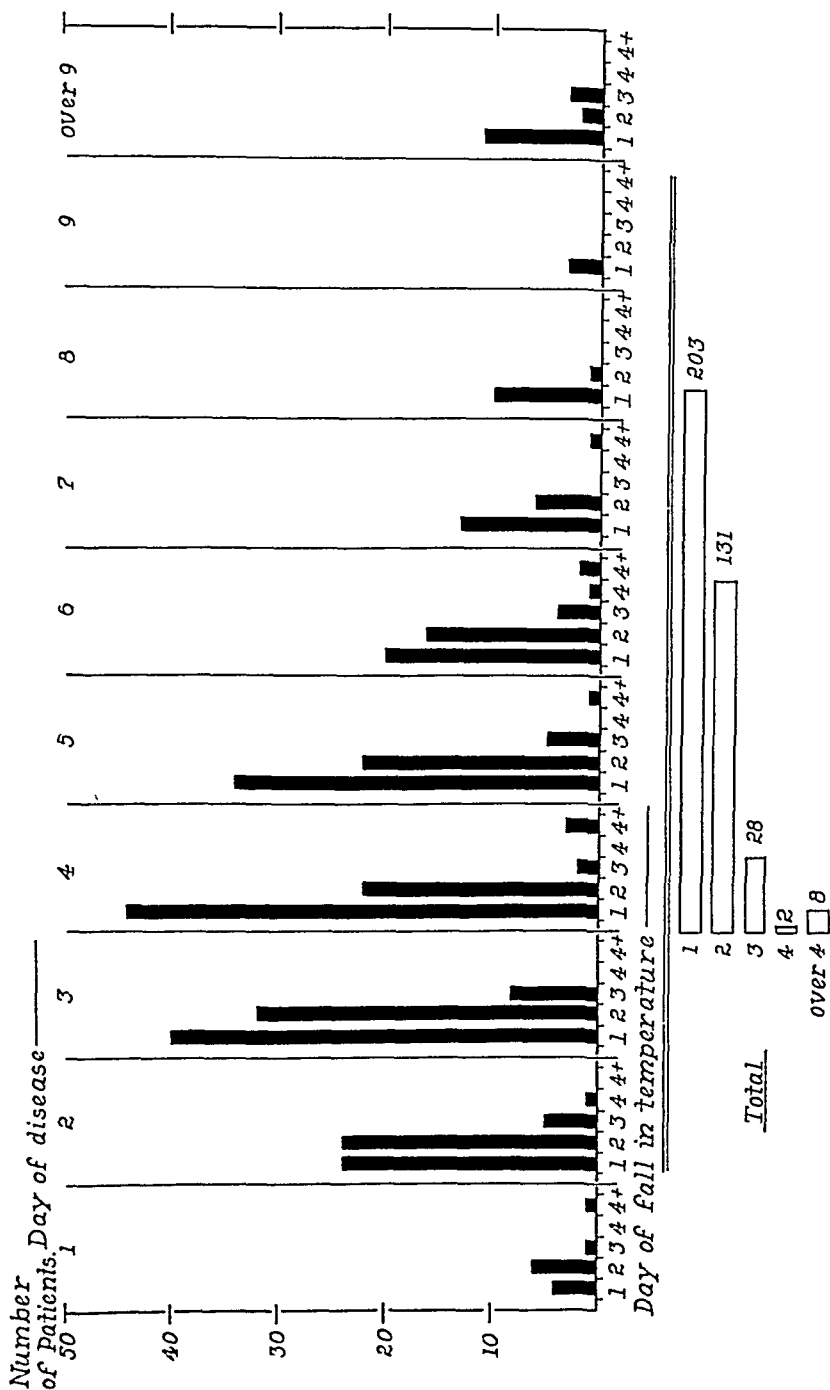


CHART 3.—Time of critical drop of temperature following initiation of sulfapyridine therapy in relation to day of disease.

In those cases that developed a spread of the infection or other complication, such as empyema, meningitis, or drug reaction, we often encountered marked elevation in the total white count several days after treatment had been started.

TABLE 6.—INCIDENCE OF COMPLICATIONS IN TYPED SERIES.

Complication.	Number.	Incidence. %.
Massive effusion	11	2.8
Empyema	5	1.3
Phlebitis	3	0.8
Otitis media	2	0.5
Meningitis	2	0.5
Total	23	5.9

Complications (Table 6). There were only 5 cases in which frank empyema developed. In 11 others that developed large pleural effusions, thoracentesis was performed for diagnostic purposes or because of mechanical difficulties with respiration. Most authorities agree that a small amount of pleural fluid usually develops in pneumococcal pneumonia. The incidence of empyema is known to vary from one series of pneumonia cases to another, depending upon the virulence and specific type of the pneumococcus. It is generally agreed that the incidence of empyema in patients with Type I pneumonia is consistently high, according to Reimann^{17b} about 13%. In our 104 cases of Type I pneumonia, there were only 2 cases of empyema. As noted in Table 2, there were only 2 fatalities in the group having complications, Patients II and IV both having empyema and meningitis. This low incidence of septic complications substantiates our belief in the ability of the sulphanilamide group of drugs to prevent the spread of an infectious process through normal tissue.

TABLE 7.—TOXIC REACTIONS IN TYPED SERIES.

Toxic reactions.	Number.	Incidence, %.
Nausea	212	53.0
Vomiting—troublesome	144	36.0
severe	23	5.8
Dermatitis	2	0.5
Acute hemolytic anemia	1	0.25
Leukopenia	2	0.5
Drug fever	2	0.5
Psychosis	4	1.0

Toxic Reactions (Table 7). The most troublesome and frequent untoward effects of the drug were nausea and vomiting. Both appeared, as a rule, during the first 24 hours of treatment; and we agree with Marshall¹⁴ that these are probably of central rather than local origin, as both have been observed following the administration of the soluble salt of sulfapyridine intravenously. In 25 patients the vomiting was so severe that drug therapy was stopped; but in no

case was this done before 12 gm. had been administered. None of these patients died. In 144 patients, the vomiting was a source of distress to the patient, but not sufficiently severe to require total cessation of the therapy. That vomiting did not necessarily hinder absorption of the drug was shown by several patients with high blood sulfapyridine levels in whom vomiting had occurred shortly after the administration of each dose. In these patients we felt that it was due to a psychic reaction caused by the unpleasant taste of the drug. No correlation was observed between the level of sulphapyridine in the blood and the development of nausea and vomiting. The following measures were adopted, all of which appeared to improve the tolerance for the drug: 1, Mixing the drug with water, fruit juices or milk; 2, administration of small amounts of sodium bicarbonate or aluminum hydroxide solution after ingestion of the drug; 3, temporary omission of treatment for 1 or 2 doses; 4, the use of barbiturates and chloral hydrate; 5, the introduction of sodium chloride and dextrose intravenously; 6, the use of nicotinic acid in daily doses of 300 to 450 mg.

Item 5 appeared to be a valuable method of lessening the severity of the nausea and vomiting as well as providing for the restoration of a normal fluid and electrolyte balance. This assumes even greater importance in the dehydrated patient in view of the recent reports of renal damage.

Nicotinic acid has been tried by us recently because McGinty, Lewis and Holtzclaw¹³ have reported that sulphanilamide reactions were relieved by nicotinic acid; it has given us encouraging results in a few patients.

The toxic reactions shown in Table 7 are similar to those associated with sulphanilamide treatment; in our experience they do not occur as frequently with sulfapyridine as with sulphanilamide. Marked leukopenia developed in 2 instances but no instance of agranulocytosis was observed. Acute hemolytic anemia occurred in only 1 patient, but in several others there was a drop in the red blood count of over 2 million and a reduction in hemoglobin up to 40%. In patients who were markedly dehydrated at the time of the first blood count and who then received adequate fluid and sulfapyridine, it is obviously difficult to evaluate the lower counts which followed. Cyanosis is likewise difficult to evaluate in a disease involving the lungs. In about 12% of our cases it was found either to have appeared or to have increased in intensity after initiation of the sulfapyridine therapy. From our experience with the cyanosis associated with sulphanilamide therapy, and aware of the work of Marshall and Walzl,¹⁵ who observed that clinical cyanosis following sulphanilamide therapy did not necessarily involve a decrease in the oxygen carrying capacity of the red blood cells, we have not felt that cyanosis following sulfapyridine therapy was an indication for withdrawal of the drug.

In only 2 patients was a diagnosis of drug fever made; this leads us to feel that we might have overlooked this type of reaction in certain cases. In not a few patients there was noted a secondary rise in the temperature following the critical fall; this we ascribed to various causes and often increased the dose of sulfapyridine. In a study of gonorrheal urethritis treated with sulfapyridine¹² a febrile reaction was observed in 7 of 80 patients, unassociated with a flare-up of the disease process. As febrile episodes in this condition are usually associated with obvious extension of the infection, it seemed highly likely that the percentage of febrile reactions to sulfapyridine was much higher than that indicated by the 2 cases recognized in the pneumonia cases. It is true, of course, that while lower doses were given to the group with gonorrheal urethritis, the patients were ambulatory and were treated for longer periods of time.

As sulfapyridine occasionally produces untoward effects, it should be used with full recognition of its toxic possibilities. It is important to follow closely the patients to whom it is being administered. The urine should be studied repeatedly for red blood cells, crystals and urobilin, and the blood picture for anemia and neutropenia. Any secondary rise in temperature must be carefully analyzed in view of the possibility of drug fever. Even greater importance than usual must be laid to the avoidance of dehydration for fear of allowing sufficient concentration of the urine to cause crystallization and development of sulfapyridine concretions within the urinary tract. Plasma chloride studies are indicated in those patients with severe vomiting and blood urea nitrogen determinations in patients in whom renal injury is suspected.

TABLE 8.—INCIDENCE AND MORTALITY AMONG AGE GROUPS IN NON-TYPED SERIES.

Age groups, yrs.	No. of cases.	No. of deaths.	Mortality, %.
12 to 19	19	0	0.0
20 to 29	18	1	5.6
30 to 39	12	0	0.0
40 to 49	20	2	10.0
50 to 59	15	1	6.7
60 to 69	12	2	16.7
70 and over	4	3	75.0
Total	100	10	10.0

Non-typed Cases (Table 8). We have also analyzed our first hundred records of pneumonia patients from whom no typable pneumococcus could be isolated. It is to be noted that these cases are not consecutive and, of course, do not necessarily fall into one group. Most of them represent patients in whom the severity of the infection warranted immediate treatment, and sulfapyridine therapy was instituted with the expectation that a specific pneumococcus would be isolated from the sputum or blood culture. In 35 cases a pneumococcus was recovered that could not be typed; in 15

the blood culture was negative and no sputum was obtained; and in the remaining 50 there was either a mixture of organisms or the predominant organism was not a pneumococcus. Blood cultures, taken in 66% of these cases, were positive in 3. In 2 of these an untypable pneumococcus was recovered and the third yielded a hemolytic streptococcus. One of the 2 patients with blood stream invasion by untypable pneumococci died, the other developed empyema but eventually recovered. The patient with streptococcus infection made an uneventful recovery.

Evaluation of the effectiveness of sulfapyridine therapy in this heterogenous group of cases is difficult. In some the drug had little or no effect. This was especially true in the staphylococcus cases and in those with atypical onset, relative bradycardia, and normal leukocyte count. In most of these patients who had typical findings of lobar pneumonia, the drug seemed as effective as in the typed cases. The complications and toxic effects encountered in the non-typed cases were comparable to those described in the typed series. Of 66 patients that had urinalyses during the period of treatment with sulfapyridine, only 3 patients showed (microscopic) hematuria.

Comment. In view of our experience thus far, sulfapyridine appears to be an effective therapeutic agent in the treatment of pneumococcic pneumonia. That the apparent success of the drug in the treatment of our patients has been influenced by a possible reduction in the virulence of the pneumococcus this year must be considered. Experience has shown that the virulence of the higher numbered types of pneumococci varies from year to year, while that of the first three types and especially Type I remains fairly constant. Our mortality rate was favorable (in the first 3 types: Type I, 5.8%, Type II, 6.8%; Type III, 16.4%). The high mortality of the Type III cases was, we believe, due to the fact that this organism selects the debilitated and aged patient. Our mortality in Type I compares favorably with the mortality of 5% in 60 other cases reported in the literature,^{1,3,5,9,11,16,18,20} and is, we believe, significant.

We have suggested certain potentially fatal reactions that might occur with the use of sulfapyridine. In our 500 cases, however, there was not one death that we believe was caused by this drug. It was equally efficacious in pneumonias due to the various types of pneumococci and in those cases in which the predominant organism was an untypable pneumococcus. This type of therapy can be instituted as soon as a diagnosis of pneumonia is made and need not wait as in specific serum therapy for the production of sputum and the typing of the organism. No patients were encountered who could not tolerate a therapeutic dose of the drug, whereas 4 of our patients had been unable to take serum because of serum sensitivity. One of them went into syncope and almost died after a small test dose of horse antiserum. Undoubtedly

had all the cases been tested for horse serum sensitivity other sensitive cases would have been discovered.

Summary. 1. A mortality of 7% is reported in a series of 400 patients with typed pneumococcic pneumonia treated with sulfapyridine.

2. Of these 400 cases, 197 were caused by the first three types of pneumococci, with a mortality of 5.8% in 104 cases of Type I pneumonia, 6.7% in 30 cases of Type II pneumonia, and 16.4% in 67 cases of Type III pneumonia.

3. Our experiences regarding dosage, influence of the drug on the course of the disease, complications and toxicity are described.

4. One hundred cases of non-typed pneumonia treated with sulfapyridine are briefly discussed.

This large series of cases was only made possible through the generosity and co-operation of a number of physicians in and around Philadelphia. The authors wish to express their appreciation to these men, to Miss Helen Lynch and to Dr. J. H. Clark for their technical assistance, and to Dr. I. S. Ravdin for his constant interest and helpful suggestions.

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THE USE OF SULPHANILAMIDE IN ACUTE SUPPURATIVE ARTHRITIS DUE TO THE HEMOLYTIC STREPTOCOCCUS.

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OBSERVATIONS made during the course of the patient's illness, which are recorded in the following case report, emphasize the value of sulphanilamide in controlling a severe type of hemolytic streptococcic sepsis. Following an attack of acute tonsillitis, the patient

developed acute glomerular nephritis with a severe degree of nitrogen retention, pneumonia, and suppurative arthritis of the knee. Sulphanilamide was administered to the patient, and a complete restoration of joint function was obtained 5 weeks after entry to the hospital. Simultaneous free sulphanilamide determinations were done on the blood and synovial fluid. During the same period, all signs of nephritis disappeared. Of considerable importance were the results of studies of stained smears of the synovial exudate with particular reference to the morphologic changes in the streptococcus. These latter observations confirmed *in vitro* studies made by others^{1,2} on the mode of action of sulphanilamide.

Case Report. J. L., a 35-year-old, white male laborer, was in good health until the sudden onset of tonsillitis. His temperature was 104° F., but his condition gradually improved, and within a few days he was up and out of doors. Two weeks after the onset, he suffered from a chill lasting 30 minutes. He attempted to keep on working but 2 days later he "ached all over," had fever, and developed a cough. A diagnosis of pneumonia was made and confirmed roentgenologically. He was confined to bed, and his left knee became swollen and painful and the urine became scanty and bloody.

He had had scarlet fever, measles, mumps, and pertussis in childhood.

On entry to the hospital, the patient appeared acutely ill and stuporous. There was an uriferous odor to his breath. The fundi appeared normal. His pharynx was reddened, but no exudate was present. The neck veins were distended. His heart was slightly enlarged to the left by percussion. There was a systolic murmur along the left sternal border. No diastolic murmur was heard. The rhythm was regular. The blood pressure was 122/74. The venous pressure in the antecubital vein of the right arm was 4.5 cm. of blood. No abnormal findings were apparent in the lungs. The abdomen was soft, and no masses were palpated. There was no edema of the extremities. The left knee, which was fixed in semiflexion, had peri-articular swelling, increased temperature of the skin, and marked tenderness on motion and palpation. There was evidence of a marked effusion into the synovial cavity.

Roentgenologic examination of his chest revealed a density in the right upper lobe, which was designated as characteristic of an infarct. Two weeks later another examination showed a normal lung field. A roentgenogram of his left knee was interpreted as showing minimal lesions involving the articular surfaces. Two electrocardiograms were interpreted as being within normal limits.

Repeated urine analyses showed a specific gravity ranging between 1.007 and 1.018. Albuminuria was present for the first 3 weeks. The sediment contained many erythrocytes and leukocytes, both of which gradually decreased in number until the time of his discharge, when only an occasional cell of each type was present. His hemoglobin was 71 % on entry (Sahli), erythrocytes 5,050,000 per c.mm., and white blood cells 14,700. He developed a progressive anemia, so that 3 weeks after entry his hemoglobin was 48 %, with 2,950,000 erythrocytes per c.mm. The white blood cells level rose to 32,600 per c.mm. while he was receiving sulphanilamide. His blood urea nitrogen level is charted in Figure 1. During the first week in the hospital it was 81 and 104 mg. %. The creatinine was 2.4 mg. % and the uric acid 6.4 mg. His total plasma proteins were 6.3 gm., with 3.4 gm. of albumen and 2.8 gm. of globulin. The carbon dioxide combining power of his blood serum was normal. The sedimentation rate of his

erythrocytes during his first week in the hospital was 111 mm. during the first hour, and 127 mm. during the second (Westergram).

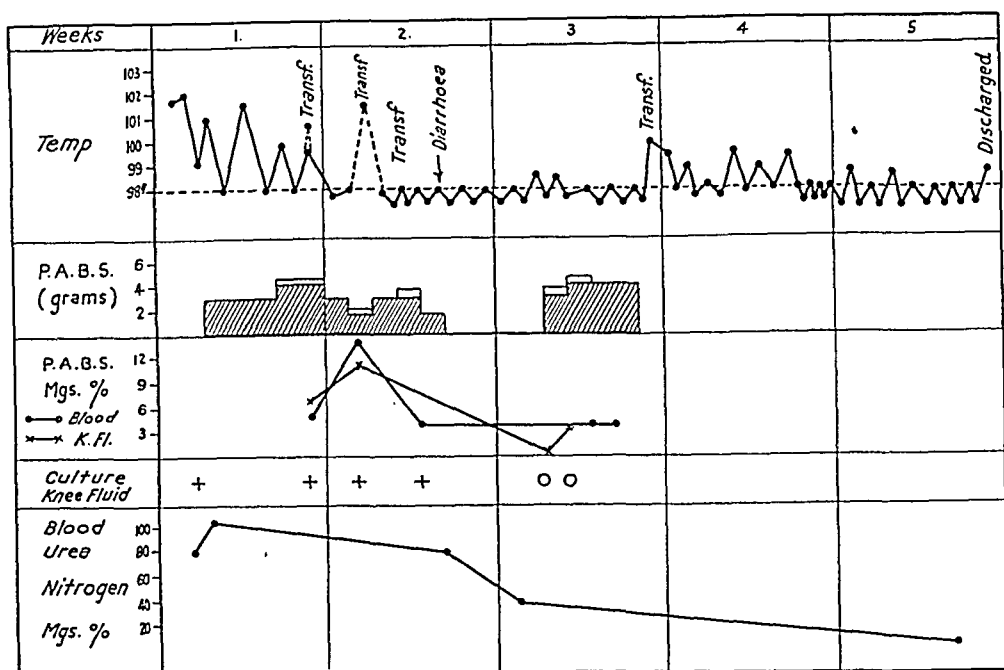


FIG. 1.—The course of a patient treated with sulphanilamide, who had a suppurative arthritis of the knee and acute glomerular nephritis.

TABLE 1.—CHARACTERISTICS OF ASPIRATED SYNOVIAL FLUID.

Date of aspiration, 1938.	Amt. in cc.	Appearance.	Culture.	Gram stain of fluid.
9-3	60	Green, thick, purulent	B. hemolytic streptococcus	Most of cells are neutrophils with occasional clasmatocyte. Short chains of Gram-positive cocci, mostly extracellular.
9-7*	80	Thick, purulent with small masses of fibrin	B. hemolytic streptococcus	Neutrophils again predominate. Most of cocci now intracellular, filling the cytoplasm of the leukocytes. Cocci remaining extracellular, stain poorly (part of chain Gram-neg.); large swollen pleomorphic cocci; "Indian club" forms.
9-9*	40	Bloody, purulent	B. hemolytic streptococcus	Some type of cell predominating. Very few cocci seen—all intracellular and none extracellular.
9-12*	15	Thin, cloudy	B. hemolytic streptococcus	No organisms seen.
9-16*	40	Purulent, thick	Sterile	No organisms seen.
9-17*	25	Thin, sero-purulent	Sterile	No organisms seen.
9-26	10	Sero-purulent	Sterile	No organisms seen.

* Following aspiration 20 cc. of 0.8% sulphanilamide in physiologic saline solution introduced into joint cavity. Drug also given orally.

The patient was under observation in the hospital for 5 weeks. Two days after entry, 60 cc. of green, thick, purulent material were aspirated from the synovial cavity of the left knee. A pure culture of a beta hemolytic

streptococcus was isolated from the fluid. The morphologic features of the fluid stained by Gram's method were studied microscopically (findings tabulated in Table 1). It should be pointed out that examination of the fluid obtained at the initial aspiration showed short chains of cocci which were extracellular. Only an occasional coccus was found within the cytoplasm of the phagocytes. Shortly after sulphanilamide therapy was instituted, the synovial fluid was examined again. At this time the cytoplasm of many neutrophils and clasmatocytes were filled with cocci. Many of the extracellular organisms showed pleomorphic changes and stained poorly. Following the initial aspiration, the patient was considerably relieved. Because of his renal failure, sulphanilamide was given cautiously. Three days after entry, he was given a total of 40 grains a day in divided doses, for 3 days. He was then given 60 grains a day. After 3 days the free sulphanilamide present in his synovial fluid was 6.3 mg. %, and in the blood 5.1 mg. Two days later the levels were 10.8 mg. % in the synovial fluid, and 12.4 mg. in the blood. Other determinations are recorded in Figure 1. The patient was also given 4 transfusions with citrated blood because of his anemia. After his first week in the hospital his temperature became normal. During the second week of sulphanilamide therapy, he developed a diarrhea. It was difficult to ascertain whether this was due to his uremia or to the sulphanilamide. The drug was omitted for several days, his diarrhea subsided, and then sulphanilamide was again administered. There was no recurrence of this diarrhea.

The patient improved considerably as to his general condition. The pain in the joint gradually subsided. Aspiration of the synovial cavity yielded sterile fluid on 2 occasions during the third week. The sulphanilamide was discontinued. He was allowed out of bed 5 weeks after entry to the hospital. He had no pain in the knee joint. At this time, there was no nitrogen retention. Roentgenologic examination showed no change in the articular surfaces. He was able to extend the leg fully, and there were 10 to 15 degrees of flexure deformity. There was some periarticular swelling and definite atrophy of the quadriceps muscle. It should be stated that at no time did he have an elevation of his blood pressure over the normal limits.

The patient was seen 4 weeks after he left the hospital. He had gained weight and he had no pain in his knee joint. Some periarticular swelling, and atrophy of the quadriceps were still present, but he was able to flex and extend completely the left lower leg. His blood urea nitrogen was normal. Urine analysis revealed no albuminuria, and the sediment contained 2 to 3 red blood cells and an equal number of leukocytes per high power field. Three weeks later, he informed us that he had returned to work.

Discussion. Suppurative arthritis due to the hemolytic streptococcus is marked by its chronicity and the destruction of joint tissue. Even when the nature of the joint changes is recognized early, and surgical drainage is instituted, recovery is usually accompanied by ankylosis. In the present case, there was a complete restoration of joint function, which we attribute to the result of sulphanilamide therapy. Prior to administering the drug, the organisms in the synovial exudate were extracellular, but after its exhibition, the bacteria were intracellular, and many of those remaining extracellular showed degenerative changes. We have never seen such an abrupt change in the position, morphology, and staining characteristics of the hemolytic streptococcus in examinations of many synovial exudates from patients not treated with sulphanilamide.

The drug was given orally and injected in solution directly into the joint cavity. Whether the latter procedure is necessary, only further experience will decide. It would appear that the free sulphanilamide level of the synovial fluid approximates that of the blood level. We have also made a similar study of the pleural exudate of a patient with a hemolytic streptococcic empyema. The same changes were observed in the stained smears before and after sulphanilamide therapy.

Gay and Clark¹ studied the mode of action of sulphanilamide by exposing hemolytic streptococci to rabbit serum containing the drug. After a period of time, stained preparations of the mixture showed the organisms to have distinct degenerative changes. The chains were markedly elongated, and the individual cocci were swollen, metachromatic, and pleomorphic. However, the distorted cells were still encapsulated, and had not lost their virulence permanently. Lockwood² in another study made similar observations. When organisms were added to sulphanilamide and serum, the first change noted in the organism was the persistence for from 8 to 12 hours of a pink capsule. The capsule normally persists for only 4 hours. At the same time, there was an increase in the size of the cocci and a tendency toward the formation of longer chains. Then there appeared irregularities in the contour of the chains, coalescence of cocci, marked pleomorphism, and transparent gaps in the chains. The study of Gram-stained smears of the exudate from the joint cavity in the present case revealed similar degenerative changes. These *in vivo* observations confirm the *in vitro* studies of the foregoing investigators.

It would appear that from the foregoing observations, and those of others³ that sulphanilamide is an effective therapeutic agent in the treatment of suppurative arthritis due to the hemolytic streptococcus.

Summary and Conclusions. 1. A patient with severe streptococcic sepsis, including tonsillitis, pneumonia, acute glomerular nephritis with nitrogen retention and suppurative arthritis of a knee joint, was treated with sulphanilamide. There was complete restoration of joint function.

2. A study of the exudate from the joint cavity obtained before sulphanilamide therapy showed short chains of cocci, mostly *extracellular*. After sulphanilamide had been administered, large numbers of cocci were *intracellular*, and the extracellular organisms were pleomorphic, and stained poorly. These observations confirm the experimental studies of others.

3. The free sulphanilamide level of synovial fluid tends to approximate the level in the blood.

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A NOTE ON THE OCULAR SYMPTOMS OCCURRING FROM MALNUTRITION IN HUMAN BEINGS.*

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RECENTLY we have described spectacular improvement in a large series of persons with pellagra, beriberi, and riboflavin deficiency following the administration of synthetic nicotinic acid, synthetic thiamin hydrochloride, and synthetic riboflavin.² After the initial improvement, the addition of these synthetic chemical substances as daily supplements to the inadequate diets of these persons is beneficial in that many of them become strong enough to work, with the result that they often buy a better diet and subsequently are restored to good health. Those whose diet remains the same have better health with these supplements than without them; nevertheless, they often remain undernourished and in ill health. This suggests that even though three essential substances, nicotinic acid, thiamin hydrochloride, and riboflavin, are supplied, the diet usually ingested by these patients must be deficient in still another substance or substances. Past experience has shown that by administering still larger amounts of nicotinic acid, thiamin hydrochloride, or riboflavin, another period of improvement could be induced,³ but we decided to keep the intake of food and of these synthetic chemical substances constant.

The present report is concerned with 50 patients treated as described above, but who had or developed ocular manifestations, characterized by severe burning, itching, and excessive dryness of the eyes. Oftentimes, the patients describe a "scum" over their eyes and state that the eyes hurt when they go into sunlight. There is granulation and extreme redness of the conjunctiva, particularly of the lower lids, and a striking degree of photophobia. The whole symptom complex is extremely variable from patient to patient and, as a rule, disappears in the late summer and returns again in the early spring. These lesions appear, irrespective of whether the deficiency developed as the result of an inadequate food intake due to economic factors or to chronic alcoholic addiction, or as the result of organic diseases which interfered with adequate nutrition.

Unpublished observations¹ on 70 unselected cases in the nutrition clinic, 20 of whom were children, showed a striking deficiency of vitamin A in the diets of 65 cases. Following the daily administra-

* This study was aided by grants to the University of Cincinnati College of Medicine from the Rockefeller Foundation, the John and Mary R. Markle Foundation, and the Martha Leland Sherwin Memorial Fund.

tion of vitamin A, in the form of carotene in oil* or as oleum percomorphum,† in amounts ranging from 10,000 to 50,000 units, these patients were able to read better, the burning ceased, and the conjunctivitis and photophobia disappeared. Following this therapy there has been, so far, little if any improvement in the dizziness, nystagmus, and dilated pupils, but the patients have reported an increase in strength and feeling of well-being.

The present studies support the hypothesis that dietary deficiency diseases in human beings are nearly always multiple in nature. They show also that certain ocular symptoms, in 50 persons who have had long-continued dietary deprivation, are corrected by the administration of carotene in oil or of oleum percomorphum.

The author is grateful to Miss Jean M. Grant and to Miss Nelwyn Huff for their assistance in this study.

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FAMILIAL POLYCYTHEMIA.

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THERE are numerous reports on polycythemia since the classical papers of Vaquez and Osler. In most instances, however, descriptions of the disease have limited themselves to individual cases. There is a paucity of well-authenticated reports on the familial and congenital incidence of this disease. This report deals with our findings in 4 cases of polycythemia vera occurring in one family.

Ambard and Fiessinger¹ claim to be the first to call attention to the *congenital* incidence of polycythemia vera. They reported the case of a female who had had cyanosis and dyspnea from birth until the onset of her menstrual life, at which time the symptoms disappeared only to reappear at the menopause. The pertinent data given show that the patient had an erythrocyte count of 7.8 million per c.mm., leukopenia, dilatation of the venous system with such congestion of the viscera that the latter had an "angiomatous" appearance. The spleen was not enlarged. From their autopsy report it would appear that the patient died with hypertensive heart disease with cardiac failure, terminal nephritis and polycythemia. There is no conclusive evidence that the patient had polycythemia early in life.

* Supplied by the S. M. A. Corporation, Chicago, Ill.

† Supplied by Mead Johnson & Co., Evansville, Ind.

In 1908, Nichamin¹⁶ reported a case of polycythemia with splenomegaly and cyanosis. He believed that he was the first to demonstrate the *familial* incidence of the disease for he states that the patient's mother and sister also had enlargement of the spleen and cyanosis. Since he failed to report analytic data on the blood of these relatives, one cannot credit Nichamin with being the first to report the familial incidence of polycythemia vera.

Bernstein³ was the first to report data on the blood of a patient and the patient's relative. The patient had an erythrocyte count of 12.5 million per c.mm. with 140% hemoglobin; his son had an erythrocyte count of 7.5 million per c.mm. with 120% hemoglobin. The father had splenomegaly and cyanosis; the son's spleen was not palpable. Bernstein's cases are perhaps the first well-established cases of familial polycythemia vera to be found in the literature.

A few years later Tancre²² reported the findings in a family in which 2 sisters had polycythemia. The patient had an erythrocyte count of 12.6 million per c.mm. with 171% hemoglobin and 17,000 leukocytes; her sister had an erythrocyte count of 6.1 million with 148% hemoglobin. Three other siblings had normal blood pictures.

In 1920, Engelking⁸ reported the incidence of polycythemia in 3 generations of one family—the grandmother, the mother and 5 children. The disease was associated with endocrine disturbances, for he found infantilism and menstrual disturbances in the children. He pointed out that the oldest child began to look "blue" at 5 years of age and that the age incidence of the polycythemia—in the 'teens—was well below the usual age incidence 35 to 55 years. A further study on this same family was made by Wieland²⁵ some 4 years later. At that time, the mother, 3 sons and a daughter showed red cell counts ranging from 8 to 12.16 million per c.mm., hemoglobins ranging from 98 to 150%, hematocrits ranging from 57 to 84% and normal white cell counts. Wieland stated that he believed the disease to be constitutional and hereditary.

In 1922, Doll and Rothschild⁷ reported their observation on a family in which the father and 2 children had polycythemia. The father, aged 44, had the following blood findings: erythrocytes, 6.15 million per c.mm.; hemoglobin, 115%; color index, 0.88; leukocytes, 6500 per c.mm.; palpable spleen; blood pressure, 200/115. Five of the 6 children had Huntington's chorea and 2 of these 5 had polycythemia, but the blood findings are very close to the upper limits of normal.

Signorelli²⁰ reported a clear-cut case of polycythemia in a male but his claim that the patient's sister also has polycythemia is less well established. The cases reported by Curschmann⁶ do not have adequate data to show that he was dealing with familial polycythemia.

In 1924, Owen¹⁷ emphasized the familial nature of the disease and

stated that "the disease is a familial one and every case should be investigated from this point of view. There may be other familial defects present also." While Owen's patient undoubtedly had polycythemia the data on the patient's brother are less convincing. Unfortunately, no blood volume studies were made.

Herz¹¹ reported his studies in 3 families in which he believed there was a familial tendency to polycythemia. He failed to report hematocrit findings, in only 1 case was the hemoglobin over 90%, and only 2 members of the 12 studied had erythrocytes well above normal limits. There is no convincing data that Herz was dealing with familial polycythemia.

Kretschmer,¹⁴ in 1925, reported 3 cases of polycythemia in one family. The children's ages were 5, 7 and 10 years. Only 1 had a barely palpable spleen. The leukocytes were well within normal limits. The onset of symptoms "Krampfe mit Bewusstlosigkeit" and "Blutsturz" occurred as early as the fourth year. There was no hypertension. The red cell counts ranged from 5.7 to 10.2 million per c.mm., and the hemoglobin ranged from 112 to 140%. These cases are clear-cut cases of familial polycythemia.

In 1926, Weil and Stieffel²⁴ reported the finding of polycythemia in a brother and sister. The brother had splenomegaly while the sister did not.

In 1933, Mussio-Fournier and Lussich-Siri¹⁵ reported the finding of polycythemia in 3 brothers. Their ages were 20, 23 and 27 years and the mother stated that of her 8 children only these 3 had the characteristic wine-colored lips since birth. The red cell counts were not high (5.58, 5.65 and 5.6 million per c.mm.) and only 1 brother had a palpable spleen. The authors stressed the congenital character of familial polycythemia. In the same year, there appeared a splendid report on familial polycythemia by Sporado and Forkner.²¹ These authors adequately reviewed the literature and concluded that there were only 6 instances of well-established cases of familial polycythemia reported in the literature, those of Bernstein,³ Tancre,²² Engelking,⁸ Doll and Rothschild,⁷ Kretschmer¹⁴ and Weil and Stieffel.²⁴ Sporado and Forkner²¹ studied a family of 10 over a period of months and concluded that 7 of the members of the family had benign familial polycythemia which they consider differs from polycythemia vera in that in the former there is no leukocytosis, eosinophilia, neutrophilia, increased basal metabolic rate or increased hemoglobin and the disease runs a benign course. They classified their patients into four groups: (a) Those with polycythemia with a palpable spleen, 4 cases; (b) those with polycythemia without palpable spleen, 3 cases; (c) those without polycythemia with a palpable spleen, 1 case; (d) those without polycythemia without a palpable spleen, 2 cases—pointing out, and quite correctly, that inability to palpate the spleen does not preclude the presence of splenic enlargement. Unfortunately

Sporado and Forkner failed to report data on the circulating blood volume and figures for circulating cell mass cannot be computed. It should be noted that no case had a hemoglobin above the upper limit of normal and in one-half the cases the mean corpuscular volume was below normal. Unlike Doll and Rothschild,⁷ Engelking⁸ and Wieland,²⁵ they found no associated family trait and suggest that the etiology of the disturbance lies in the defect of the germ plasm.

Method. Non-protein nitrogen and sugar were determined by the method of Folin,⁹ serum calcium by the Clarke-Collip modification of the Kramer-Tisdall method,⁵ serum protein by the micro-Kjeldahl modification of Howe's method.¹² Circulating blood and plasma volume were determined by the method of Rowntree, Brown and Roth.¹⁹ Hemoglobin estimations were done by the Sahli method and checked by the oxygen capacity method of Van Slyke.²³

The data reported here were obtained on 11 members of a family of 13—2 siblings were not available for examination. The mother stated that of her 11 children, only 4 (Cases 1 to 4) had "red faces" from the time of birth. None of the children had any significant disease in their past histories. There was no evidence of factors which might initiate a secondary polycythemia—physical examination, Roentgen ray studies and spectroscopic examination of the blood failed to reveal congenital heart disease, extensive pulmonary lesions or the presence of abnormal blood pigments. The environmental factors were similar for all members of the family.

TABLE 1.—CLINICAL DATA ON THE 4 CASES.

Case No.	Age, yrs.	Sex.	Blood pressure.	BMR.	Blood Wass.	Spleen.	Remarks.
1	11	F	110/70	-5	Neg.	? palpable	Good health, ruddy face and hands; suffused mucous membranes.
2	13	F	100/80	-18	Neg.	Not palpated	Little's disease; small in stature; ruddy complexion.
3	16	M	125/80	-15	Neg.	Not palpated	Robust; reddened mucous membranes.
4	18	F	118/75	-12	Neg.	Not palpated	Apprehensive; slightly suffused mucous membranes.

Table 1 summarizes some of the observations on the cases with polycythemia. There was no evidence of hypertension; the blood Wassermann reaction was negative in all cases; the spleen was barely palpable in only 1 case; the metabolic rate was normal in Case 1 and below normal in the other 3 cases. All 4 children had a ruddy complexion and the only physical abnormality noted was the presence of Little's disease in Case 2. The bleeding time,

coagulation time, clot retraction, platelet count and icteric index were within normal limits in all cases. Spectroscopic examination failed to reveal the presence of abnormal pigments.

Table 2 shows that there was no significant alteration in the erythrocyte count, hemoglobin content, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration of 7 of the members of the family (Cases 5 to 11). In contrast to these normals there are rather marked changes in the blood pictures of Cases 1 to 4. These 4 children had erythrocyte counts ranging from 7.48 to 8.80 million per c.mm., and hemoglobins ranging from 21 to 24.3 gm. per 100 cc. of blood. The hematocrits are approximately 150% of normal. The mean corpuscular volumes, mean corpuscular hemoglobins and mean corpuscular hemoglobin concentrations were within normal limits.

TABLE 2.—ERYTHROCYTE PICTURE.

Case No.	Age, yrs.	Sex.	Erythrocytes, mil./c.mm.	Hemoglobin, gm./100 cc.	Hematocrit, %.	Mean corpuscular volume, cu. μ .	Mean corpuscular hemoglobin, micro-micrög.	Mean corpuscular hemoglobin con- centration, %.
1	11	F	8.80	24.3	65	74	27.6	37.4
2	13	F	7.80	21.0	64	77	27.0	32.8
3	16	M	7.60	22.0	69	91	29.0	31.8
4	18	F	7.48	22.0	61	82	29.4	36.0
5	7	M	5.01	13.8	38	76	27.5	36.3
6	9	M	5.51	12.5	41	74	22.7	30.5
7	19	F	4.29	14.5	36	83	33.8	40.3
8	23	F	4.63	14.0	38	82	28.0	37.0
9	25	F	4.27	12.8	41	96	29.0	31.2
10	45	F	4.50	13.7	37	82	30.4	37.0
11	49	M	4.21	16.0	40	95	37.7	40.0

Chart 1 graphically illustrates the results of the blood volume studies. The circulating cell volumes of Cases 5 to 11 with normal red counts show normal circulating cell, plasma and total circulating blood volumes. The 4 children with the high erythrocyte counts (Cases 1 to 4) had marked increases in the volume of circulating cells per kilo of body weight. In Cases 1, 2 and 4, the increase in circulating cell volume was approximately double the normal value and occurred at the expense of the circulating plasma volume since the circulating cell volume increased without increase (above normal) in the total circulating blood volume. In 1 case (Case 3) the circulating cell volume was as great as the *total* circulating blood volume (three times as great as the normal circulating cell volume) of any of the other patients examined. This patient

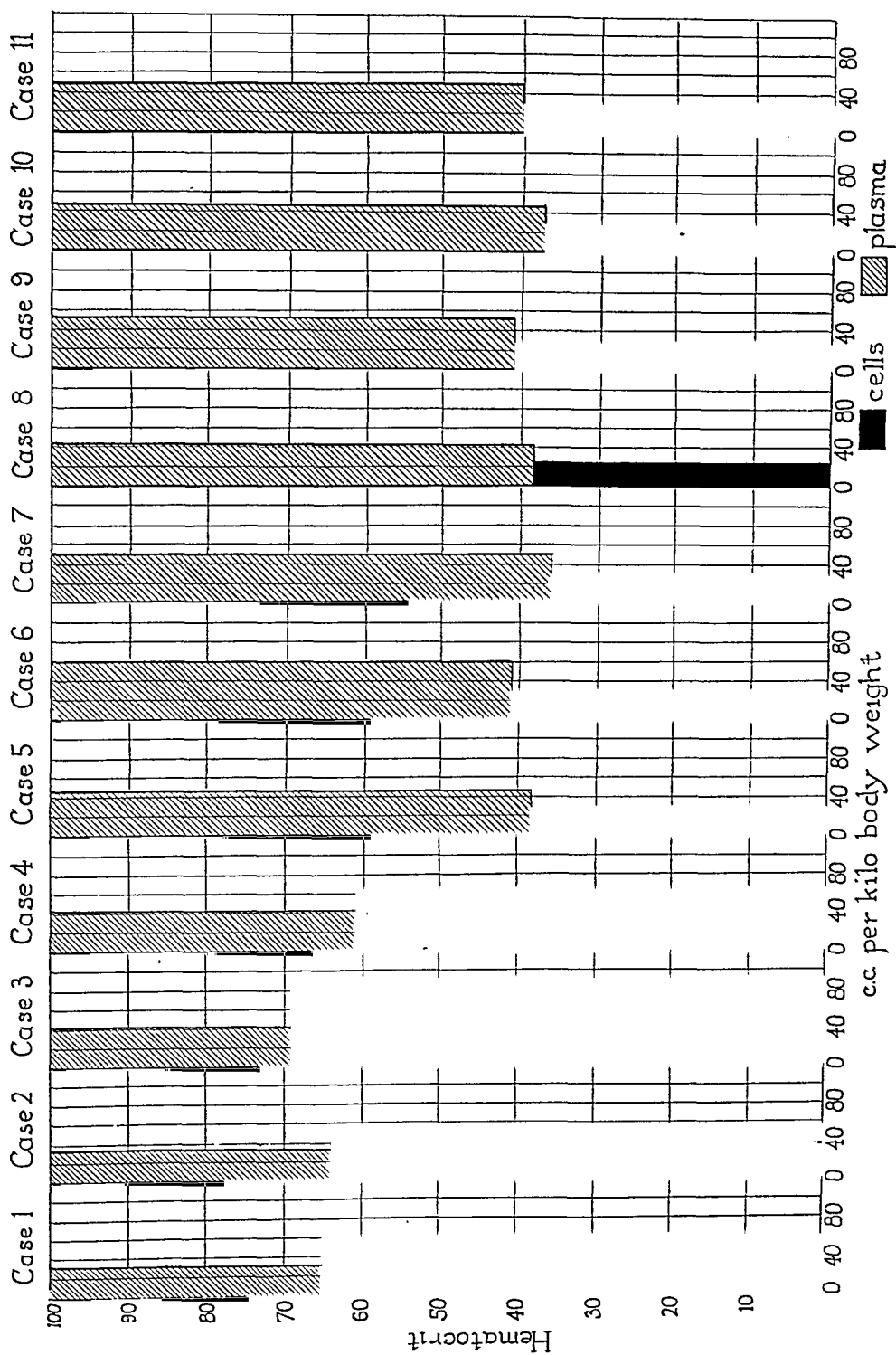


CHART 1.—Blood volume studies

had a total circulating blood volume 133 cc. per kilo of body weight. The greatly increased circulating cell mass is a common characteristic of Cases 1, 2, 3 and 4, and satisfy the criteria recently laid down by Haden¹⁰ for the diagnosis of polycythemia vera.

In contrast to the common finding of leukocytosis with preponderance of neutrophils in polycythemia vera, our cases (Table 3) showed normal or subnormal leukocyte counts with no abnormality of the differential pattern. Similar blood pictures are found in the majority of cases of familial polycythemia reviewed in this paper. Sporado and Forkner,²¹ *e. g.*, found essentially normal leukocyte and differential counts. It would appear that the factor (or factors) increasing the level of circulating erythrocytes accomplishes this purpose without interfering with the level of circulating leukocytes.

TABLE 3.—LEUKOCYTE PICTURE.

Case No.	Total leukocytes per c.mm	Neutrophils, %.	Eosinophils, %.	Basophils, %.	Small lymphocytes, %.	Large lymphocytes, %.
1 . . .	7200	60	2	2	30	6
2 . . .	4800	63	2	1	30	4
3 . . .	4800	62	3	0	34	1
4 . . .	4600	45	5	1	47	2
5 . . .	6500	38	5	0	51	6
6 . . .	6800	65	0	0	32	3
7 . . .	7200	63	2	1	30	4
8 . . .	7300	61	3	0	36	0
9 . . .	5100	62	0	1	31	6
10 . . .	6500	63	1	0	28	8
11 . . .	8400	55	0	0	43	2

The blood sugar, non-protein nitrogen and serum proteins were normal, although the latter tended to approach the upper limit of normal. Isaacs¹³ reported a high blood uric acid (6.9 mg. %) in a case of polycythemia vera and pointed out that the level of endogenous uric acid metabolism may be raised in this disease because of disintegration of the nuclei of not only the leukocytes but also of the erythrocytes. The blood uric acid was normal in our patients. Increased endogenous formation of uric acid need not be expected in untreated cases of polycythemia vera for if the level of circulating blood cell mass is established, the rate of destruction of erythrocytes may be no faster than in the normal individual; on the other hand, dramatic reduction of the circulating cell mass by methods increasing the breakdown of cell (phenylhydrazine, Roentgen ray, etc.) may be associated with high levels of blood uric acid.

TABLE 4.—BLOOD CHEMICAL FINDINGS.

Case No.	Non-protein nitrogen, mg. %.	Sugar, mg. %.	Uric acid, mg. %.	Serum calcium, mg. %.	Serum protein.		
					Alb., gm. %.	Glob., gm. %.	Total, gm. %.
1 . . .	40	83	2.18	10.5	5.05	2.73	7.78
2 . . .	30	80	3.00	10.2	4.00	2.80	6.80
3 . . .	34	85	2.80	9.8	4.30	2.92	7.22
4 . . .	28	75	2.23	10.0	4.10	3.10	7.20

The serum calcium findings of Brown and Roth⁴ prompted us to do serum calcium and serum protein determinations. Brown and Roth found hypercalcemia, 11.1 to 18.1 mg. % (average 14.3 mg. %) in a series of cases of polycythemia studied at the Mayo Clinic. They noted further that following reduction of the number of circulating erythrocytes (by phenylhydrazine therapy) they obtained normal or subnormal serum calcium values. They offered no convincing explanation for the hypercalcemia. Rabinowitch¹⁸ and Benedict and Turner² failed to find hypercalcemia in polycythemia vera. The serum calciums in our cases were within normal limits.

Summary. Four cases of polycythemia occurring in one family are described. Data on the circulating blood volume in familial polycythemia are reported for the first time. Since cases of familial polycythemia seem to differ from classical cases of polycythemia vera in that elevated metabolic rate, neutrophilic leukocytosis, splenomegaly and symptoms referable to this disease are not a striking feature of familial polycythemia, it has been assumed that familial polycythemia is not the same as polycythemia vera. In these cases of polycythemia, however, the red cell mass was of the magnitude of that found in polycythemia vera. Since Haden¹⁰ finds increase in cell mass to be characteristic of polycythemia vera, it now seems justifiable to include "familial polycythemia" in the group of cases of polycythemia vera.

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**INFLUENCE OF THE PERIPHERAL CIRCULATION IN THE UPPER
EXTREMITY ON THE CIRCULATION TIME AS MEASURED
BY THE SODIUM CYANIDE METHOD.**

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ALTHOUGH the circulation time has been studied by a variety of methods in the last few years the influence of the capillary circulation on the velocity of the venous return to the heart has been neglected. In the sodium cyanide, histamine, saccharine, calcium gluconate and decholine methods the reagent is usually injected into the antecubital vein and the length of time that it takes the injected substance to travel from the site of injection to the reacting organ is determined; sodium cyanide measures the antecubital to carotid sinus time.^{3a} When the antecubital vein alone is used as the site for injection, these methods do not separate the elbow to heart circulation time from the heart to reacting organ time.

It is well known that local conditions can influence the peripheral circulation in the parts drained by the antecubital veins, namely, the forearm and hand, without appreciably altering the circulation of the body as a whole. Thus if slowing of the total blood flow in one forearm and hand appreciably decreases the velocity with which blood from these regions returns to the heart, the circulation time as measured from this extremity will be prolonged though no pathologic disturbance of the circulation is present. The object of this study was to determine whether changing the amount of blood flowing through the upper extremities by varying the local temperature would appreciably alter the antecubital to carotid sinus circulation time as measured by the injection of sodium cyanide.

Method. The circulation time was determined by the sodium cyanide method as described by Robb and Weiss.^{3a} From 0.2 to 0.4 cc. of a 2% solution of sodium cyanide (4 to 8 mg.) was injected into one of the antecubital veins. The time elapsing between the injection and the first deep breath was recorded by a stop watch. The upper extremities were placed at heart level and the peripheral circulation was varied by placing the hands in plethysmographs containing water which could be maintained at any desired temperature. When one extremity was to be kept warmer than the other, measurements were not made until the difference in temperature of the forearms was detectable by palpation. When it was necessary to use

stasis to enter the vein, the injection was delayed until the reactive hyperemia induced by the venous occlusion had subsided. Sufficient time was allowed between determinations for the pulse rate to return to the resting level.

Results. The circulation times in 6 subjects are given in Table 1. Five of these subjects had normal cardiovascular systems; the sixth, G. K., had rheumatic heart disease with mitral regurgitation but no signs of decompensation. The circulation time in the cool arm in these 6 cases averaged 32.3 seconds and in the warm arm 18.5 seconds (average difference 13.8 seconds). The differences noted in Table 1 persisted as long as the hands and forearms remained at their respective temperatures, regardless of the number of determinations made. In each case the circulation time in the cool extremity was sufficiently prolonged to be considered pathologic by the usual standards. Robb and Weiss^{3a} found that the cyanide circulation time in 35 normal subjects varied from 9 to 21 seconds; the average time was 15.6 seconds. In 5 of our 6 cases the circulation time as measured from the warm hand was within normal limits. In the sixth, F.R., a healthy male aged 22, the generalized constrictor effect of the cold water seemed to predominate and the circulation time in the warmer extremity in this subject was somewhat prolonged. An attempt was made to produce reactions of the same intensity from each arm by increasing the amount of cyanide injected in the cooler arm (Table 1). The reactions from the cooler arm, however, tended to be less intense than those obtained from the warmer arm with the more rapid peripheral circulation.

Discussion. The antecubital to heart circulation time is greatly influenced by the condition of the circulation in the portion of the forearm and hand that is drained by the antecubital veins. It is not clear whether the circulation in the forearm or in the hand, singly or combined, is of paramount importance in influencing the circulation time. Grant and Pearson² have shown that on moderate heating of the body vasodilatation occurs chiefly in the hand and that the forearm shows little increase in flow. Since the venous return from the hand passes through the forearm veins, however, an increase in flow in the hand alone is reflected by an increase in the amount of venous blood flowing through the forearm.

TABLE 1.—CIRCULATION TIMES AS DETERMINED BY INJECTION OF SODIUM CYANIDE IN THE ANTECUBITAL VEINS. EFFECT OF LOCAL TEMPERATURE OF UPPER EXTREMITY.

Subject.	Cool hand.			Warm hand.		
	Temperature of hand (C.).	Cc. of cyanide solution.	Circulation time (sec.).	Temperature of hand (C.).	Cc. of cyanide solution.	Circulation time (sec.).
F. C. R.	25°	0.40	47	40°	0.25	27
E. M.	25°	0.35	30	40°	0.30	18
G. K.	24°	0.40	35	40°	0.20	19
E. S.	30°	0.30	25	40°	0.20	16
A. S.	23°	0.35	30	43°	0.25	13
H. F.	24°	..	27	42°	..	18

It will be noted that there was considerable variation in the circulation time in the warm arms. No attempt was made to duplicate standard conditions for each experiment. The hand temperatures and the length of time that the hands were immersed in the water varied in different experiments. In addition, the room temperature was not controlled. As the circulation time was determined from both the right and left antecubital veins within the space of a few minutes, each subject served as his own control to show that the difference in circulation time from the right and the left antecubital veins resulted from local changes in the peripheral circulation and not from gross changes in the general circulation.

Blumgart and Weiss^b in their study of the antecubital to heart circulation time in normal subjects by the radium C method found that the average elbow to heart time varied in normal subjects from 2 to 14 seconds. They also noted that the variation in the velocity of the venous blood in the arm in the same subject at different times and in different subjects was greater than the variation in the velocity of blood flow through the lungs. Robb and Weiss^{3b} also found that in normal subjects an index of velocity of venous blood returning from the elbow, determined by measuring both the antecubital to carotid and the jugular to carotid circulation times by the injection of sodium cyanide, showed more variation than the jugular to carotid circulation time. These variations may well have occurred, at least in part, because the local temperature of the arm was not controlled.

The amount of sodium cyanide required to produce a clear-cut response depends on the rapidity of the circulation and the sensitivity of the carotid sinus. In our subjects, assuming the carotid sinus sensitivity to be constant over a short period of time, the amount required to produce a definite response varied with the temperature of the upper extremity. In the cooler arm with the slower peripheral circulation there was more time for dilution of the sodium cyanide solution during its passage to the heart and therefore larger doses were necessary. Likewise in subjects whose circulation times are prolonged because of cardiac failure, larger doses of radium C¹ or of histamine⁵ are required than in normal subjects with a more rapid circulation. Robb and Weiss,^{3b} however, called attention to the fact that the amount of sodium cyanide needed to produce a definite response in subjects with cardiac failure is only approximately three-fourths that required by normal subjects. They pointed out that in congestive failure an increased irritability of the respiratory center to cyanide usually more than compensated for the greater "stringing out" of the sodium cyanide caused by the slow circulation.

Over a period of years a few normal subjects have been encountered in whom satisfactory responses to sodium cyanide were not obtained.⁴ In some of these subjects, a satisfactory response was obtained on the following day, indicating that the carotid sinus was sensitive to

cyanide stimulation. In these cases, the lack of response may have been due to a marked decrease in peripheral blood flow resulting from reflex arteriolar constriction of emotional origin. It is also possible that in certain instances the cyanide itself produces local irritation and spasm in the vein used for injection.

These observations show that the local temperature of the extremities plays an important part in determining the velocity with which blood returns to the heart. Before a given circulation time obtained by the injection of sodium cyanide into the antecubital vein can be considered as indicative of cardiac or other change, one must be certain that prolongation is not the result of a decrease in the peripheral blood flow induced by cold extremities.

Summary and Conclusions. 1. In 6 subjects the elbow to carotid sinus circulation time was measured in each arm by the sodium cyanide method. The two upper extremities were kept at different temperatures by immersing one hand in water at 40 to 43° and the other hand in water at 23 to 30° C. The circulation time in the cool arm averaged 32.3 seconds; in the warm arm 18.5 seconds.

2. The state of the peripheral circulation in an extremity influences the velocity of venous flow. Therefore, in an accurate study of the circulation time from the antecubital vein the temperature of the upper extremity must be controlled.

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RENAL ARTERIOLONECROSIS WITHOUT PAPILLEDEMA.

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It is a well-known clinical fact that the differential diagnosis between the terminal uremia of glomerulonephritis and that due to necrotizing nephritis (renal arteriolonecrosis) is extremely difficult.⁶

There is hardly one symptom or sign of renal dysfunction present in one that cannot be present in the other, such as hyperchromic microcytic anemia, uremic pericarditis, ulcerative colitis or azotemia. Even with respect to age incidence the two conditions overlap, for it must not be forgotten that renal arteriolonecrosis occurs like glomerulonephritis in middle age, early adult life and also in children.⁵

In contrast to the many equivocal diagnostic findings mentioned above, the presence of papilledema is regarded by some authors¹⁻⁴ as pathognomonic of renal arteriolonecrosis (necrotizing nephritis). Fishberg² goes so far as to state that without papilledema the diagnosis of renal arteriolonecrosis is not justifiable. Although we concede that the retinal vessels are the mirrors *par excellence* of the status of the kidney arterioles, we cannot subscribe to the extreme view that without papilledema there can be no necrotizing nephritis.

Of the 5 cases at this hospital in the last 4 years which showed renal arteriolonecrosis at autopsy, only 2 had papilledema. In the other 3, the eyegrounds showed mild retinal arteriosclerosis, *but no papilledema*. This autopsy experience differs so from that of the school of Volhard and Fahr that we feel it worthwhile to publish in some detail the last 3 cases.

Case Abstracts. CASE 1.—Malignant nephrosclerosis without papilledema. A. S. (No. 97254), admitted, December 18, 1937; died, January 18, 1938. A white female, aged 42, gave a history of hypertension and headaches for 5 years. She had precordial pain for many years, and shortness of breath for 2. She was admitted to Bellevue Hospital in October, 1937, complaining of dizziness and weakness of 3 weeks' duration and swelling of the eyes lasting 3 days, associated with fever and increased dyspnea. At this time, her blood pressure was, systolic 272, diastolic 140, N.P.N. 35, and the urine showed a few red and white blood cells. She was discharged, November 20, 1937, with the diagnosis of hypertensive cardiovascular disease; secondary anemia, cause undetermined.

Five days before admission she first noticed bloody urine with polyuria and nocturia, being forced to awake 5 or 6 times a night. With the onset of hematuria, the patient complained of severe frontal headaches and impairment of vision by "black and green spots."

On physical examination the patient appeared drowsy. The heart was moderately enlarged to the left, with a harsh systolic murmur heard all over the precordium. The blood pressure was systolic 270, diastolic 170. The ophthalmologic consultant (Dr. F. S. Newman) found the "*retinal arteries extremely thin, thread-like and tortuous. Pallor of both discs show atrophy of secondary nature. No papilledema.*"

The urine showed a fixation of specific gravity between 1.010 and 1.014, innumerable red blood cells (4+ benzidine), many white blood cells, occasional hyaline and granular casts. R.B.C. 3,460,000, with 66% Hb.; N.P.N. was 94; total proteins 6.37; albumin-globulin ratio 1.26. Wassermann test negative. Roentgen ray showed concentric hypertrophy of the heart associated with sclerosis of the aortic arch. Cystoscopy revealed a low-grade cystitis that accounted for the bloody urine.

Radiant heat and light were applied to the kidney region, without any relief. Three days before exitus a rapidly developing parotitis appeared;

a pericardial friction rub was audible; urea frost covered the face and body, and the patient died, January 18, 1938.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut): Malignant sclerosis of kidney (arteriolonecrosis); hypertrophy of left ventricle; arteriolosclerosis of different organs. Characteristic arterial changes in pancreas, intestinal canal, myocardium and uterus; diffuse hemorrhages in gastro-intestinal tract; bronchopneumonia.

Kidneys each weigh 105 gm. The capsule is thin and strips with ease. Numerous small, pinhead hemorrhages are present on the pale, yellowish-pink, uniformly coarsely granular surface. On sections, the cortex of each kidney averages 5 to 7 mm. in width.

Microscopically. Corresponding to the granulation of the surface, atrophy of kidney tissue is found with fibrosis. In places, very severe hyaline droplet change is seen. Atrophy of tubules is widespread. A number of glomeruli show more or less necrosis and overgrowth of the capsular epithelium. While in places the diseased glomeruli form groups, the distribution appears entirely irregular in others, with normal and severely diseased glomeruli close to each other. Corresponding to the hemorrhagic spots, glomeruli are seen which are almost entirely destroyed by hemorrhage. Tubules in the surroundings of these glomeruli are widely distended with blood. In spite of some search, no hemorrhagic or necrotic lesions are found in the arterial vessels of the kidneys, the picture being principally that of atherosclerotic intimal thickening. The smallest arteries and afferent vessels show diffuse, very severe arteriosclerosis with much necrosis. Arteriolonecrosis is likewise found in the cut sections of the ovary, uterus, myocardium, intestines, and is unusually marked in the liver, pancreas and hypophysis.

Comment. Pathologically, this case is of interest (Fig. 1) because of the widespread distribution and the severity of the arteriolonecrosis, without any signs of papilledema. The pathologic picture is characteristic of necrotizing nephritis, and the clinical diagnosis too would have been the same if the absence of papilledema had not militated against it in our minds, and suggested the erroneous diagnosis of secondary contracted kidney due to glomerulonephritis.

CASE 2.—Malignant nephrosclerosis without papilledema. S. B. (No. 76793), admitted, September 25, 1935; died, October 12, 1935. A 47-year-old white female, a known hypertensive for the past 10 years. One year ago she had a right hemiplegia from which she recovered. There was a year's history of polyuria and nocturia, and a week's history of generalized aches and pains, tremors and marked drowsiness.

On admission, the patient was disoriented with a urinous odor to the breath and twitching of the extremities. The heart was moderately enlarged. Gallop rhythm was occasionally heard, as was a pericardial friction rub. Blood pressure was systolic 260, diastolic 160, with little variation in level. The urine showed persistently albumin, many granular casts, many white blood cells and rare red blood cells. Specific gravity was fixed between 1.006 and 1.008. N.P.N. varied from 111 to 166. Spinal fluid was under normal pressure.

Dr. S. Slomka, the ophthalmologic consultant, reported "*thin and tortuous retinal vessels, otherwise eyegrounds are normal.*"

Intravenous magnesium sulphate failed to reduce the very high blood pressure. Urea frost appeared on the face, and the patient died on the seventeenth day of hospitalization.

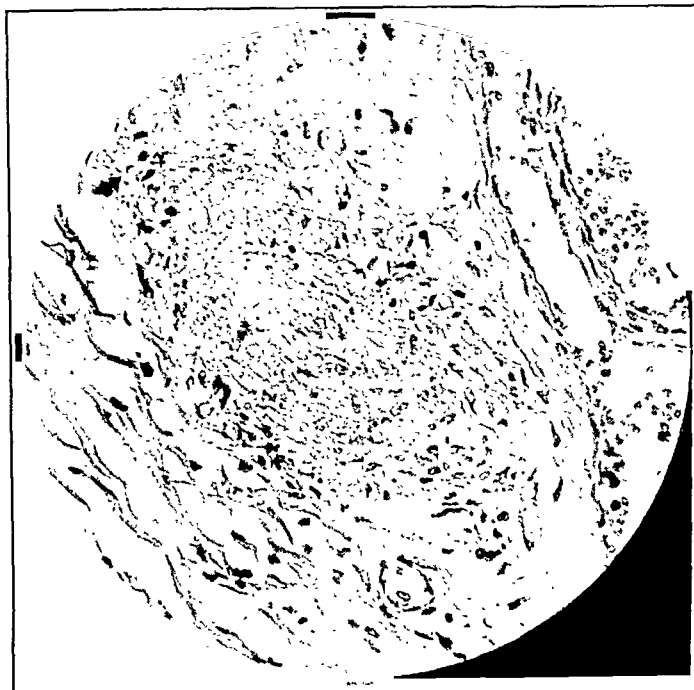


FIG. 1.—A necrotic arteriole in the stomach characteristic of lesions found in various organs. (The lesion in the stomach rather than the kidney is shown because the latter photographed poorly.)

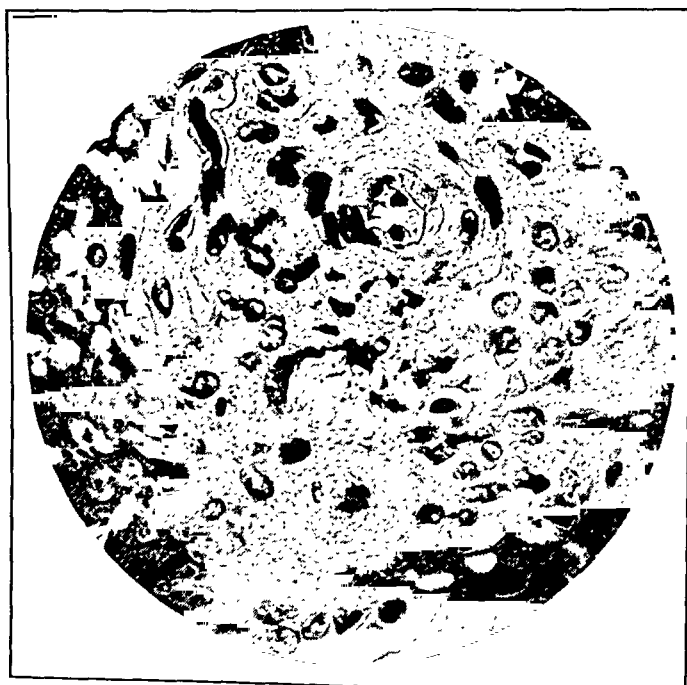


FIG. 2.—Necrosis in wall of renal afferent vessel. Fragments of chromatin visible.

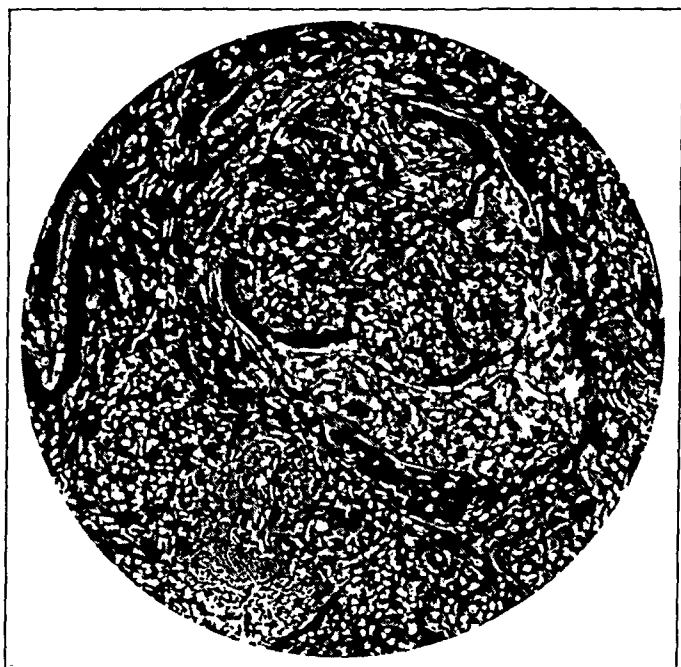


FIG. 3.—Necrotic afferent vessel. Thrombus with large crescent.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut): Arteriolosclerosis of kidneys (malignant sclerotic type); hypertrophy of left ventricle; dilatation of left ventricle and auricle; mitral insufficiency; diffuse fatty change of myocardium; atheromatosis of sinuses of Valsalva, coronary arteries and ascending aorta; periarteritis nodosa in perisuprarenal fat tissue; multiple aneurysms of medium-sized arteries in the omentum; inflammatory process in myocardium; small scars of myocardium with isolated arteriolar lesion (perhaps rheumatic); moderate arteriolosclerosis of pancreas, suprarenals, intestine and uterus.

The kidneys are 75 and 100 gm. in weight. Both strip easily out of their thin, smooth capsules, leaving finely granular surfaces. The cut surfaces show very small cortices (0.4 cm. in width), and indistinct outline between cortex and medulla. There is much dark purplish-red mottling due to congestion and small hemorrhagic areas. The renal artery is thick-walled and shows atheromatous patches.

Microscopically (Fig. 2), the picture is that of arteriolosclerosis with much reduction in the number of glomeruli. There is necrosis of afferent vessels with severe fatty changes in these vessels and neighboring arteriolar portions. There is fatty change in many glomeruli but in few tubules. Some glomeruli show a breaking up of their tissue into hyaline droplets and amorphous hyaline pieces. Corresponding to hemorrhage seen on the surface, hemorrhage is found mostly within distended tubules. The largest arterial branches in the kidney give the ordinary picture of arteriosclerosis to different degrees. There is necrosis of small arteries not only in the kidney tissue proper but also in the hilar fat issue. One focus of acute periarteritis has been found (the one in the suprarenal fat tissue).

Comment. This case is of unusual pathologic interest in that it represents arteriolosclerosis and arteriolonecrosis of the kidneys with a focus of acute periarteritis nodosum in the suprarenal fat tissue. There is, however, no vascular lesion in the kidneys which in any way resembles periarteritis nodosum. The case is considered one of malignant nephrosclerosis, the arteriolar sclerosis and fibrosis being apparently much more extensive than the minimal changes in the eyegrounds would indicate. With a history of hypertension of 10 years' duration in a woman of 47, and with 1 year of threatened renal decompensation, finally with fixation of specific gravity and azotemia, the clinical picture of the terminal stage of malignant hypertension (necrotizing nephritis) was clear enough without investigation into the eyegrounds. The findings in the fundi were so meagre that several of the physicians who observed this patient did not dare venture the diagnosis of necrotizing nephritis which looked most probable from every other point of view.

CASE 3.—Chronic glomerulonephritis and severe renal arteriolonecrosis without papilledema. R. B. (No. 62564), admitted, March 30, 1934; died, April 4, 1934). A 46-year-old white female with history of swelling of the face of 1 week's duration. She had hypertension at least 3 years, swelling of the feet for 2 years, frequent headaches, dizziness, dimness of vision and spots before the eyes for several months before admission. The present illness began 2 weeks after a mild upper respiratory infection with swelling of the face, hands and feet. Two nights before admission the patient became somewhat comatose, had numerous twitchings of the extremities, and did not void for 2 days.

The patient appeared to be *in extremis* from the start. There was a marked uremic odor to the breath. N.P.N. was 150; urine showed specific gravity 1.012, 4+albumin, many red blood cells and numerous white blood cells. Blood pressure was systolic 150, diastolic 105. Spinal tap revealed the spinal fluid under markedly increased pressure.

The ophthalmologic consultant (Dr. F. Newman) reported that "*aside from small attenuated vessels and occasional small petechial hemorrhages, the fundi are normal in all respects.*" The patient died 5 days after admission.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut.) Chronic glomerulonephritis with severe arteriolonecrosis; arteriolonecrosis in liver; hypertrophy of left ventricle, subdural and subarachnoid hemorrhage; stasis in spleen, liver and lower lobes of lungs.

The kidneys weigh 135 and 140 gm. They strip with slight difficulty from their capsule, and are coarsely granular. The cortex is narrower than usual. The pyramids are short, dark purple with some red streaks. The renal arteries are thick-walled.

Microscopically (Fig. 3), the number of glomeruli in the later phase of glomerulitis is relatively small. All gradations are seen from glomeruli with only slight overgrowth to others where the capsular overgrowth represents the bulk of the glomeruli. There is distinct fatty change in the much distended tubules. On the other hand, in the blood-vessels the fatty change is scant. This is the more astonishing since *unusually severe arteriolonecrosis is found*. This necrosis is so marked that it is easily seen even on low magnification. Only a few of the necrotic arterioles are surrounded by inflammation. The small and medium-sized arteries mostly do not show severe lesions. Some of them have intimal proliferation. In several the media is very thick. Many irregular areas of fatty change are seen in the interstitial tissue.

A necrotic arteriole with inflammation similar to the one found in the kidney is seen in a section from the liver. Representative sections from myocardium, brain, aorta, and lung do not show arteriolonecrosis.

Comment. This is a case of chronic glomerulonephritis with such severe arteriolonecrosis that after the most careful microscopic study, the concomitant presence of both conditions had to be recognized.

Ophthalmologically in this case there was only thinning and attenuation of the retinal vessels and occasional petechial hemorrhages, otherwise the fundi were normal. Apparently there was no indication in the eyegrounds of the widespread arteriolonecrosis which took place in the kidneys and liver.

Discussion. It is not intended in the report of the above cases to belittle the importance of papilledema as the leading diagnostic sign in renal arteriolonecrosis due to necrotizing nephritis or other forms of hematogenous kidney disease. It brings out the important fact, however, that shortcuts in diagnosis and aphorisms may disturb rather than help our clinical thought. In all 3 cases at the bedside we felt the clinical picture was that of necrotizing nephritis, and the only hesitation about going on record with certainty as to the diagnosis was the absence of papilledema. We feel, therefore, that when the history and clinical manifestations favor the diagnosis of necrotizing nephritis, the absence of even so important a leading sign as papilledema should not deter us from making the diagnosis.

Another point of interest in our studies is that of the 5 postmortem cases proven to be necrotizing nephritis, the 3 which did not show papilledema were all females. Such a small series does not justify speculative reasoning. It suggests, nevertheless, that in arteriolar sclerosis and necrosis we may have a different selective affinity in the female than in the male. We know that arterial and arteriolar disease in general affects the two sexes differently, that coronary sclerosis is much more frequent in the male than in the female. This holds true for arteritis, thrombo-angiitis obliterans, and pulmonary arteriolitis. On the other hand, the cerebral vessels are affected a little more frequently in females than in males. It is possible, therefore, that the arteriolonecrotic process attacks the retina less frequently in the female than in the male. Thus renal arteriolonecrosis is less likely to be associated with papilledema in the female than the male.

Summary. Three cases are presented which showed at autopsy extensive arteriolar necrosis of the kidneys and which clinically failed to demonstrate even a faint suggestion of papilledema. All were females. In 2, the condition was pure necrotizing nephritis secondary to malignant hypertension. The third was a combination form where marked necrosis of the renal arterioles was engrafted on the picture of chronic glomerulonephritis.

These cases make untenable the clinical dictum that without papilledema there is no renal arteriolonecrosis.

We take this opportunity to express our indebtedness to Drs. I. W. Held and Alfred Plaut, without whose constant help this clinico-pathological study would have been impossible.

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CHANGES IN LACTIC ACID, pH AND GASES PRODUCED IN THE BLOOD OF NORMAL AND SCHIZOPHRENIC SUBJECTS BY EXERCISE.*

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THE possibility that dysfunction in the oxidative mechanisms might play a rôle in the schizophrenic process has been suggested

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by previous investigations from these laboratories (Hoskins⁴). It has been shown that the blood volume per square meter body surface of these patients is smaller than that of normal men (Looney and Freeman^{7a}) and that it circulates at a slower rate (Freeman²). It should be expected, therefore, that if the body tissues of the schizophrenic patient were metabolizing at a rate equal to the normal subject, differences in the oxygen and carbon dioxide content of the arterial and venous bloods of the two groups would be found. We (Looney and Freeman^{7b}) have not been able to detect such differences and have therefore been forced to conclude that some disturbance in the oxidative functions must occur in the tissues. Further evidence of this dysfunction is seen in the inverse relationship which has been found to exist in our patients between the lactic acid and reduced glutathione content of the blood. We find that a fairly high correlation occurs between the two factors in the patients while no such relationship exists between them in normal subjects. This finding would seem to indicate that the removal of lactic acid is dependent on two or more catalysts, one of which is glutathione. In the patients, a disturbance of the other mechanisms throws a greater burden on the glutathione, and therefore a relationship between its level and that of lactic acid is found. In the normal subject, however, the glutathione can vary without affecting the lactic acid because of the presence of other mechanisms for its oxidation.

In order to gain further information concerning the production and removal of lactic acid we have studied the changes in its level in the venous blood following moderately strenuous exercise in 35 normal and 35 schizophrenic subjects. At the same time we have also determined the pH of the venous blood, and the oxygen and carbon dioxide content.

Method. The subjects, after resting for 30 minutes in bed, had a control sample of blood taken in an oiled syringe according to the technique of Looney and Childs.⁶ They then ran up and down a flight of stairs 3.15 meters high for 10 minutes, making about 4 trips per minute. At the end of this period they again reclined in bed for 2 hours, and samples of blood were taken at 2 minutes, 4 minutes, 8 minutes, and so on, up to 128 minutes. The first and last samples after the exercise were taken in oiled syringes and the others in oxalated serum bottles.

The samples were analyzed for lactic acid in duplicate by the method of Friedemann, Cotonio and Shaffer³ on 3 ml. of blood with the precaution that the air was drawn through wash bottles, the first containing bisulphite and the second acid permanganate, to remove any bisulphite binding and oxidizable substances. Blood gas determinations were made by the manometric method of Van Slyke. The pH determinations were made on whole blood at 38° C. with the glass electrode and electron tube potentiometer built according to the specifications of Stadie *et al.*¹⁰

Results. In Table 1 the results for the variables pertinent to the lactic acid production are tabulated. We find that there is a significant difference between the two groups with respect to age, body

weight, meters run in 10 minutes, kilogram meters of work performed, lactic acid produced per meter, and lactic acid produced per kilogram meter per minute.

TABLE 1.—THE EFFECT OF EXERCISE ON VARIOUS FUNCTIONS IN SCHIZOPHRENIC AND NORMAL SUBJECTS.

Variable.		N.	Min.	Max.	Mean.	Standard deviation.
Age	Pts.	35	18	48	26.6 \pm 1.0	5.6 \pm 0.64
	Nor. cont.	33	18	31	22.1 \pm 0.6	3.1 \pm 0.39
Body wt. (kg.) . .	Pts.	35	49	85	61 \pm 1.4	8.1
	Nor. cont.	35	56	82	68 \pm 1.2	6.9
Meters run in 10 ¹ .	Pts.	35	85	154	110 \pm 2.8	16.2
	Nor. cont.	35	79	167	120 \pm 2.7	15.7
Kg./min.	Pts.	35	474	1064	690 \pm 24.6	143
	Nor. cont.	35	490	1091	812 \pm 19.5	114
Control L.A. . . .	Pts.	35	6.3	18.2	12 \pm 0.5	3 \pm 0.36
	Nor. cont.	35	5.8	21.3	12.5 \pm 0.7	4.3 \pm 0.52
Max. L.A. reading .	Pts.	35	22.9	147.6	77.37 \pm 4.20	24.5 \pm 3
	Nor. cont.	35	23.4	132.5	68.31 \pm 4.79	27.923 \pm 3.4
Increase of L.A. (mg.)	Pts.	35	11	135	65 \pm 4.2	24.4
	Nor. cont.	35	10	103	56 \pm 4.7	27.5
L.A. rise per meter .	Pts.	35	0.12	1.53	0.6 \pm 0.04	0.25
	Nor. cont.	35	0.13	1.01	0.46 \pm 0.04	0.22
L.A. rise per kg. body wt.	Pts.	35	0.20	2.33	1.07 \pm 0.08	0.49
	Nor. cont.	35	0.16	1.78	0.81 \pm 0.08	0.44
L.A. rise per kg. m. min.	Pts.	35	0.02	0.26	0.097 \pm 0.007	0.04
	Nor. cont.	35	0.01	0.13	0.065 \pm 0.005	0.03

A consideration as to which of these variables might be expected to be of primary importance in relation to lactic acid production yields the following information. The difference in age, though significant, is not held to influence lactic acid production as there is no correlation between lactic acid and age in the age ranges observed in our samples.

The difference in weight is not brought about by the inclusion of extreme values, but is actually due to a tendency for the patients to be lighter than the normal subjects. This difference in itself would not be expected to alter significantly the lactic acid production, but it is of some importance in a consideration of the lactic acid production per kilogram meter of work performed. The patients, being lighter, would have had to run 13 more meters than the normal subjects to produce an equivalent amount of kilogram meters of work. This would amount to approximately one more

trip than the normal subjects made, whereas actually the patients averaged one less trip. As the number of trips made was significantly lower and the body weights were also significantly lower, it follows that the kilogram meters of work performed was, in turn, significantly lower. This value of 690 ± 24.6 kg./m./min. for the patients as compared with 812 ± 19.5 kg./m./min. for the normal subjects was not due to the inclusion of a few extremely low values for the patients as contrasted with the normal subjects, but to a significant shifting of the distributions as a whole. Actually, 60% of the patients gave values of less than 700 kg./m./min.; whereas only 8.5% of the normal subjects fell below this figure. The mean of the control value of lactic acid for the patients of 12.02 mg. per 100 ml. of blood was almost identical with that of 12.51 mg. per 100 ml. for the normal subjects. The difference in the standard deviations is due to the fact that the values for the normal subjects were spread rather flatly throughout the entire range, while those for the patients were grouped together around the mean.

The increase in lactic acid was 65 ± 4.2 mg./100 ml. for the patients against 56 ± 4.7 mg./100 ml. for the normal subjects. This difference of 9 mg./100 ml. was not significant. It should be noted, however, that the number of meters run by the normal subjects was approximately 10% greater than the distance covered by the patients. As at this rate of exercise the lactic acid production is almost directly proportional to the work performed for any *given individual*, it follows that had each individual performed 10% more work the mean lactic acid would have been raised approximately 10% to 71 or 72 mg. and that the difference between the patients and the normal subjects would have been highly significant. For different individuals, however, there is no relation between the work performed and the amount of lactic acid produced when the exercise is moderate. Thus we find that the relation between lactic acid production and work performed by the normal subjects gives a correlation coefficient of only 0.38.

When the two groups are compared with respect to the lactic acid produced per meter run there is a significant difference between the patients with a mean value of 0.60 ± 0.04 mg. and the normal subjects whose mean value was 0.46 ± 0.04 mg. Likewise, on the basis of lactic acid produced per kilogram meter of work per minute the difference between the value of 0.097 ± 0.007 mg. for the patients and 0.065 ± 0.005 mg. for the normal subjects is highly significant.

These results give definite indication that the schizophrenic patients, as a group, show a marked muscular inefficiency in regard to lactic acid production for a given amount of work than does a group of normal subjects. The difference cannot, however, be ascribed to the schizophrenic process *per se* but only, at present, to the concomitant physical condition which can be expected in such a group. In this regard, it is to be noted that the normal

subjects were unemployed men who were hired to act as controls and lived in the same environment and received the same diet as the patients.

We have no means of determining the exact degree of training in the two groups, but some indication may be found in the fact that the changes in pulse rates taken in 23 members of each group showed no significant difference. Thus we find that the absolute rises in pulse rates per kilogram of work meter were 0.084 ± 0.008 for the patients and 0.069 ± 0.005 for the normal subjects.

The second question to be answered is whether the rate of lactic acid removal is essentially different in the normal and schizophrenic subjects. In order to determine this the means of the increases in lactic acid were plotted against time. As has been proven by the work of Margaria and his associates,^{8,9} the lactic acid concentration after it has reached its maximum value decreases at a rate proportional to the excess of lactic acid in the blood. The curve which it traces is given by the equation:

$$L_t = 10^{a+bt}$$

where L_t is the excess concentration of lactic acid at time t after the maximum reading.

a is a constant which is determined by the maximum value reached by the lactic acid.

b is a constant which is always negative and is a measure of the rate at which the lactic acid is removed from the blood.

This formula does not hold immediately after the exercise ceases but begins to apply after about 4 minutes. In conformity with the findings of Margaria, Edward and Dill, we have found that in many instances the lactic acid concentration does not reach a maximum immediately on termination of exercise but may continue to increase for 4 to 5 minutes. For this reason we have taken for our initial value the maximum concentration of lactic acid and figured our time of recovery from this point. We have taken for our resting value the lowest point reached by lactic acid during the experiment. The observations were then fitted by the method of least squares to the curve $\log L_t = a + bt$. The constants derived were then substituted in the original formula and gave the following equations: For the normal subjects $L_t = 10^{1.74} - 0.015 t$ and for the patients $L_t = 10^{1.80} - 0.013 t$

The difference between the b coefficients for normal and schizophrenic subjects was found not to be statistically significant. The standard error of b was found to be 0.00137 for the normal subjects and 0.00109 for the patients.*

It would appear from a consideration of our values that the removal of excess lactic acid in human subjects at rest is fairly constant

* For the curve fitting I am indebted to Mr. R. Dorfman. The method of calculation involved in these determinations will be given on request to any interested readers.

and takes place at such a rate that one-half of the lactic acid of the body is removed in approximately 20 minutes. The value of the b constant of 0.015 ± 0.00137 for our 35 normal subjects agrees well with that given by Magaria and his coworkers^{8,9} ranging from 0.015 to 0.020. While the production of lactic acid varies greatly with different individuals because of differences in muscular efficiency, degree of training, and so on, its removal during rest is independent of these factors.

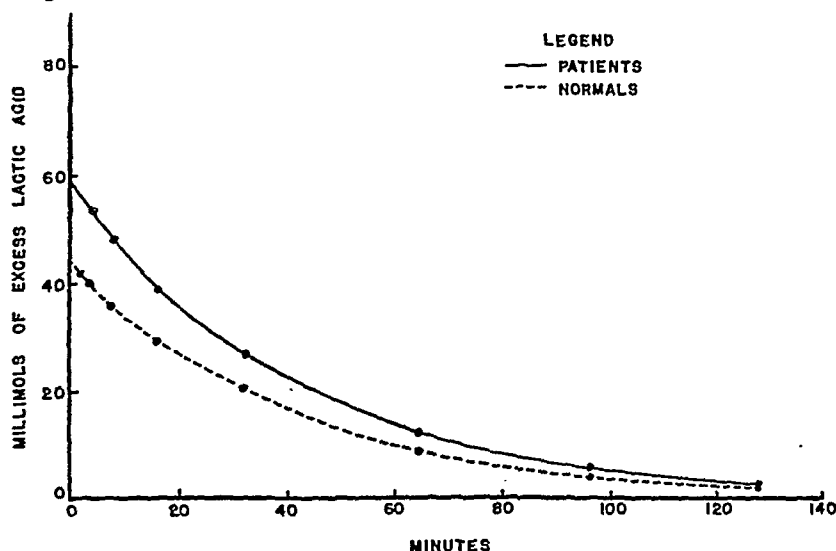


FIG. 1.—Rate of removal of lactic acid. — Patients $L_t = 10^{1.74 - 0.015t}$
 Normal $L_t = 10^{1.80 - 0.015t}$.

TABLE 2.—OXYGEN, CARBON DIOXIDE AND pH CHANGES DURING EXERCISE.

		Control reading, vol. %.	4 minutes after exercise, vol. %.	2 hours after exercise, vol. %.
O ₂	35 patients	11.5	15.9	11.2
	35 normals	10.5	15.5	11.2
CO ₂	35 patients	57.2	41.1	56.3
	35 normals	57.8	42.5	56.2
pH	35 patients	7.44	7.35	7.46
	35 normals	7.44	7.36	7.47

The changes in the oxygen and carbon dioxide content of the venous blood before and after exercise are given in Table 2. It will be noted that the values obtained for both normal and schizophrenic subjects are practically identical. In each case there was an increase in the oxygen content of the venous blood immediately after exercise. This change is unquestionably due to the more rapid circulation rate resulting from the exercise. In 2 hours the oxygen levels have returned to the preëxercise levels. The carbon dioxide levels decrease in both groups to about the same extent, the patients showing a decrease of 16.1 vol. % from the initial value of 57.2 vol. % and the normal subjects a drop of 15.3 from 57.8 vol. %. A high

inverse correlation was found to exist between the two gases, the coefficient for the patients being -0.80 and for the normal subjects -0.81 .

Previously we have shown (Looney and Freeman^{7b}) that under basal conditions there is a discrepancy in the relationship between venous oxygen and carbon dioxide in the patients as contrasted with normal subjects. We now find that this discrepancy has vanished after exercise. Whereas the normal subjects show no appreciable difference in the correlation coefficients in the two states, giving a value of $r = 0.76$ in the basal state and -0.81 after exercise; the patients, on the other hand, under the stimulation of the exercise give an increase in the coefficients from -0.47 in the basal state to -0.80 . This is an example of the ability of the schizophrenic patient to become more like the normal subject as the result of a temporary stimulus.

The values obtained for the pH agree within 0.01 of a pH unit for schizophrenic and normal subjects both before and after exercise. The determinations were made by means of the glass electrode, which when checked with the hydrogen electrode on phosphate buffers agreed within 0.005 of a pH.

The fall in pH of 0.08 is somewhat more than that of 0.05 reported by Dill, Talbott and Edwards¹ for their 10 subjects, but can probably be accounted for by the difference in the work performed. Their subjects ran on the level at a rate of 9.3 km. per hour for 20 minutes and showed an average increase of about 25 mg. % of lactic acid, which was less than one-half of the average difference for our subjects. Similarly, their subjects showed a fall in carbon dioxide of 7.3 vol. % which was less than one-half that shown for ours. Within 2 hours after exercise the average pH had returned to slightly more alkaline levels than in the initial reading, the patients giving a value of 7.46 and the normal subjects one of 7.47.

The correlation coefficients given in Table 3 are derived from an analysis of covariance.* This technique permits obtaining estimates of the correlation which obtains on the average within an individual. Such an intra-individual correlation is biologically more meaningful than a group correlation, since biologic processes take place within the individual only (Jellinek⁵). The coefficients of Table 3 all refer to intra-individual relations. Since a common trend, such as created by the common factor of exercise, may create correlation between two biologically uncorrelated variables, or may at least boost the relationship far above the true inherent correlation, it becomes necessary to obtain estimates of the correlation which is independent from this trend. Such an estimate is obtained from the residual covariance. In the left-hand column are the net correlations between the variables after the trend due to the exercise is eliminated. This use of trend elimination is well

* I am indebted to E. M. Jellinek for the following correlation analysis.

illustrated in the case of the relationship between lactic acid and oxygen. As a result of the exercise both lactic acid and venous oxygen are increased. The uncorrected correlation coefficients found were 0.66 for the patients and 0.69 for the normal subjects. However, after correcting for the trend, we find that the coefficients for both the patients and the normal subjects have practically vanished. Thus we see that while the uncorrected coefficients would indicate a fairly high degree of relationship between lactic acid and oxygen content of venous blood, actually the two variables are completely independent of each other.

TABLE 3.—CORRELATION COEFFICIENTS AND REGRESSION EQUATIONS IN SCHIZOPHRENIC AND NORMAL SUBJECTS.

		Net intra-individual corrected for trend due to exercise.		Intra-individual uncor- rected for trend.	
		r.	r.		
L.A. and CO ₂	Pts.	-0.62	CO ₂ = 57.0-0.16 L.A.	-0.95	CO ₂ = 59.9-0.25 L.A.
	Nor. cont.	-0.81	CO ₂ = 58.19-0.21 L.A.	-0.96	CO ₂ = 60-0.27 L.A.
L.A. and pH	Pts.	-0.61	pH = 0.46-0.0015 L.A.	-0.92	pH = 0.47-0.0017 L.A.
	Nor. cont.	-0.64	pH = 0.48-0.0018 L.A.	-0.87	pH = 0.48-0.0018 L.A.
CO ₂ and pH	Pts.	+0.12	pH = 0.36+0.001 CO ₂	0.85	pH = 0.10+0.006 CO ₂
	Nor. cont.	+0.58	pH = 0.10+0.006 CO ₂	0.83	pH = 0.09+0.006 CO ₂
CO ₂ vs. O ₂	Pts.	-0.54	CO ₂ = 60.2-0.67 O ₂	-0.80	CO ₂ = 78.5-2.10 O ₂
	Nor. cont.	-0.54	CO ₂ = 61.9-0.79 O ₂	-0.81	CO ₂ = 76.8-1.99 O ₂
O ₂ vs. L.A.	Pts.	0.01	O ₂ = 12.3+0.001 L.A.	0.66	O ₂ = 10.5+0.68 L.A.
	Nor. cont.	0.12	O ₂ = 11.9+0.20 L.A.	0.69	O ₂ = 10.2+0.76 L.A.

It will be noted that the *uncorrected coefficients* in Table 3 are strikingly similar for both patients and normal subjects in regard to all variables. In the case of the relationship between lactic acid and carbon dioxide it was found that an increase of 1 m.Eq. of lactic acid was accompanied by a drop in carbon dioxide of 1 m.Eq. in the patient and 1.07 m.Eq. in the normal subjects. As the fall in total carbon dioxide occurs almost completely at the expense of the bicarbonate, and since Dill *et al.*¹ have shown that there is only a very slight change in the carbon dioxide tension of the blood during exercise, this would indicate that 1 mol. of bicarbonate was neutralized for each mol. of lactic produced. These findings do not agree with those of the above investigators as they recorded an increase in lactic acid of 1.57 m.Eq. as opposed to a drop of 2.11 m.Eq. in bicarbonate. It seems probable that this discrepancy may be accounted for by the difference in the severity of the exercise, the washing out effect from the increased ventilation playing a greater rôle when the exercise is less severe.

Here again the greater rigidity in the carbon dioxide system, shown by the patients in our previous studies (Looney and Freeman^{7b}), is noted in the net intra-individual correlations, the patients showing a small degree of dependency and accounting for a smaller decrease in carbon dioxide for each millimol of lactic acid produced.

Even more striking is the difference shown between the carbon dioxide decrease and the fall in pH. Under exercise the two groups

give almost identical values for their regression equations and correlation coefficients; but when these are corrected for the trend due to exercise to give the net relationships which should exist under ordinary conditions, we find that the normal subjects show practically no difference in the regression equation but a lower correlation coefficient, 0.58 instead of 0.83. The b coefficient for the pH is not affected, a change of 0.0062 being given for each vol. % of CO_2 as against 0.0064 after exercise. The patients, on the other hand, show a very great difference in the two states. Under stress their performance is practically identical with that of the normal subjects, giving a correlation coefficient of 0.85 and a b coefficient in the regression equation of 0.0061. When the effect of exercise is eliminated the dependency of pH on CO_2 almost completely vanishes, the correlation coefficient becoming 0.12 and the change in pH becomes entirely unpredictable from the carbon dioxide values. The relationship between lactic acid and pH remains very similar for both patients and normal subjects and is relatively little affected by exercise.

Summary. The gases, pH and lactic acid were determined in the venous blood of 35 normal and 35 schizophrenic subjects before and after running for 10 minutes up and down stairs.

The mean of work performed by patients was 690 ± 24.6 kg./m./min., that for the normal subjects 812 ± 19.5 kg./m./min. The increase of lactic acid was 65 ± 4.2 and 56 ± 4.7 mg. respectively. The patients produced 0.097 ± 0.007 mg. lactic acid per kg./m./min. which was significantly higher than that of 0.065 ± 0.005 mg. for the controls.

The pH of the blood of the patients gave: control 7.44, after exercise 7.35, at end 7.46; of normal subjects 7.44, 7.36, 7.47. For the patients the O_2 values were 11.5, 15.9 and 11.2 vol. % and the CO_2 values 57.2, 41.1 and 56.3 vol. %; for the normal subjects the corresponding values were 10.5, 15.5 and 11.2 and 57.8, 42.5 and 56.2 vol. %.

The rate of disappearance of lactic acid was the same for both groups and dependent only on the blood level. Equations fitted to the curve for removal of lactic acid were $L_t = 10^{1.80 - 0.013t}$ for the patients and $L_t = 10^{1.74 - 0.015t}$ for the normal subjects. For normal subjects, about one-half of the excess lactic acid will be removed in 20 minutes during rest after the exercise.

A high negative correlation was found between lactic acid and carbon dioxide, after exercise the coefficients being -0.95 for the patients and -0.96 for the normal subjects. Between lactic acid and pH a similar effect was found with coefficients of -0.92 for patients and -0.87 for normals. While the high correlation 0.85 between CO_2 and pH appearing in the patients after exercise nearly vanishes when the trend due to exercise is eliminated, that in the normal subjects is relatively little affected.

As a result of the stress from exercise the carbon dioxide mechanisms of patients tend to approach more nearly the action of the normal subjects.

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THERAPEUSIS OF EXPERIMENTAL TYPE I PNEUMOCOCCIC MENINGITIS IN RATS.

COMPARATIVE THERAPEUTIC RESULTS OBTAINED WITH SULPHANILAMIDE, SERUM, AND COMBINATION THERAPY.

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HERETOFORE therapeusis of experimental pneumococcic meningitis involving lavage through quadruple puncture^{26a,b} or intracarotid injection of antiserum-optochin mixtures¹⁵ while showing promise, has not been very successful. Adaptations of these experiments and other forms of treatment, have not significantly altered the mortality of clinical pneumococcic meningitis as judged by recent reviews of the subject.^{11,28,29} Within the last year, however, reports^{1,3,7,14,16,17,19,21-23,27,30} of cures with sulphonamide compounds in 23 cases of pneumococcic meningitis have renewed hope for an effective treatment.

Additional support for this outlook is to be found in the generally favorable results obtained with sulphanilamide therapy in experimental pneumococcic infections.^{6b} Although this therapeutic action is not of as high an order as that observed against infections caused by hemolytic streptococci or meningococci, and is more pronounced

in rats and rabbits than in mice, it has been consistently effective in pneumococcic pneumonia^{5a,b,9a,b} and peritonitis²⁴ in rats.

More recently, we^{6,10} have shown that sulphanilamide therapy in Type II pneumococcic meningitis of rats resulted in 54 to 73% survivals, whereas none of the untreated rats survived. Inasmuch as it has been demonstrated^{4,5b,9b} that therapy with sulphanilamide plus specific antiserum gave better results than either therapeutic agent alone, it was thought of interest to use this combination therapy in experimental pneumococcic meningitis of rats. Accordingly, this report presents results obtained in Type I pneumococcic meningitis of rats treated with (a) sulphanilamide, (b) horse antipneumococcic serum, (c) rabbit antipneumococcic serum, and (d) a combination of sulphanilamide and rabbit serum.

Method and Results. Meningitis was produced by intracranial inoculation of a properly diluted 18-hour broth culture of a Type I (Neufeld) pneumococcus. A 3 mm.-long, 25-gauge needle, attached to a tuberculin syringe, was pushed to the hilt through skin and skull of etherized rats at a point about 4 mm. to the left of the sagittal suture and halfway between eye and ear. About 0.1cc. of the inoculum, which consisted of a 10^{-5} or 10^{-4} dilution of culture, was then slowly injected.

Data obtained in the present experiments confirmed previous work which demonstrated that meningitis and bacteremia were well established 6 hours after the inoculation. Histologic sections of the brains of rats killed at various intervals following inoculation showed, in addition to ecchymoses, irregularly scattered, small foci of mononucleated cells and a few neutrophils in the pia. These were found as early as the second hour, at which time cultures from the lumbar region of the cord were generally positive. Treatment, consisting of 100 mg. of sulphanilamide orally, or 333 units of antiserum intraperitoneally, or both together, was administered after the bacteremia was established.

The following 3 experiments were performed:

I. Infection with slightly less than 10 fatal doses and initial treatment delayed 7 hours following infection.

II. Infection with about 10 fatal doses and initial treatment delayed 12 hours following infection.

III. Infection with about 100 fatal doses and initial treatment delayed 7 hours following infection.

I. Infection with slightly less than 10 fatal doses and initial treatment delayed 7 hours following infection:

A series of 58 rats was inoculated with a 10^{-5} culture dilution, as described above. In addition, 2 rats were inoculated with a 10^{-6} dilution and 3 with a 10^{-7} dilution of the same culture for the purpose of titration. Both 10^{-6} and one of the 10^{-7} rats were dead in 5 days.

The infected animals were divided into 4 groups of 11 each and a control group of 14. All treatments were begun 7 hours following infection. One group was treated orally with 100 mg. of sulphanilamide* twice a day for 2 days and once daily for 6 more days. A second group received 333 units of horse antiserum† intraperitone-

* Kindly supplied by the Monsanto Chemical Company, St. Louis, Mo.

† Kindly supplied by E. R. Squibb & Sons, New York.

ally, followed by similar treatments on the second and third days. The third group was similarly treated with concentrated rabbit antiserum.* The fourth group was treated with a combination of sulphanilamide by mouth and rabbit serum intraperitoneally as in the groups where these therapeutic agents were used alone.

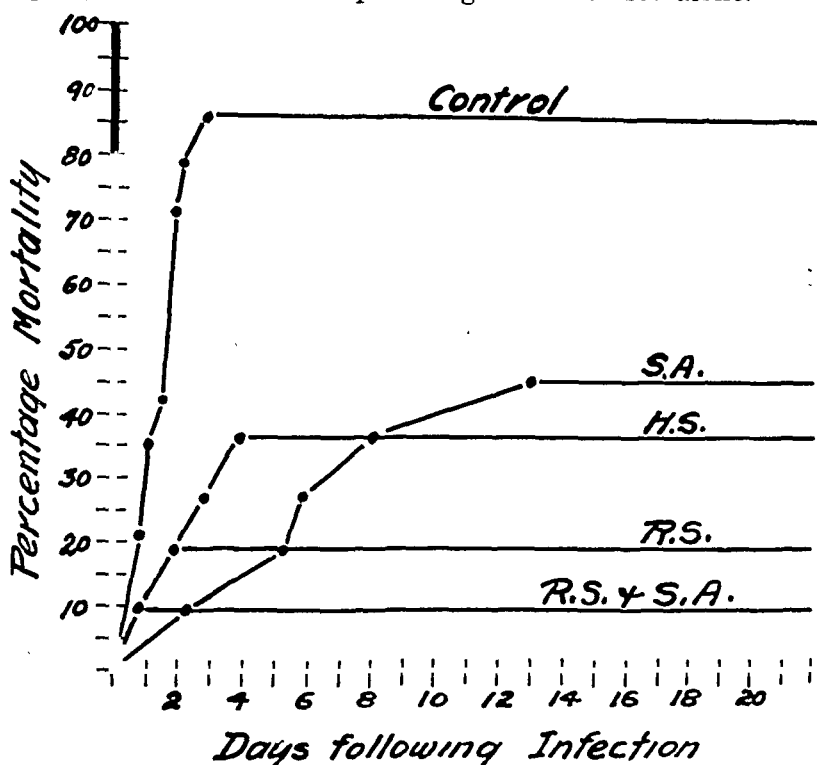


FIG. 1.—MORTALITY CURVES OF RATS INFECTED WITH LESS THAN 10 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 7 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of a 10^{-5} broth dilution of an 18-hour broth culture intracranially. *Treatment:* Controls: 14 rats, no treatment. S. A.: 11 rats, 100 mg. of sulphanilamide orally twice daily for 2 days and once daily for 6 following days. H. S.: 11 rats, 333 units of horse antipneumococcus serum intraperitoneally for 3 successive days. R. S.: 11 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 3 successive days. R. S. and S. A.: 11 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

Results. The results are shown graphically in Figure 1. The mortality rate of the control group was 85.7%; of the sulphanilamide group, 45.5%; of the horse serum group, 36.4%; of the rabbit serum group, 18.2%; and of the combination treatment group, only 9.1%. Fatalities in the sulphanilamide group showed a greater increase in survival time than was seen in the other groups.

II. *Infection with approximately 10 fatal doses and initial treatment delayed 12 hours following infection:*

A series of 60 rats was infected with a 10^{-5} culture dilution as in the preceding experiment. Three titration rats, given one-tenth of

* Kindly supplied by E. R. Squibb & Sons, New York.

the infecting dose, died in 46 to 94 hours, whereas only one titration rat of 3 given one one-hundredth of the infecting dose died (51 hours). Positive cultures were obtained from the spinal cords (distal lumbar portion) and heart blood of 5 infected rats killed at the time treatment was begun.

The remaining 55 rats were divided into 4 groups. One group of 13 served as untreated controls, a second group of 14 was treated

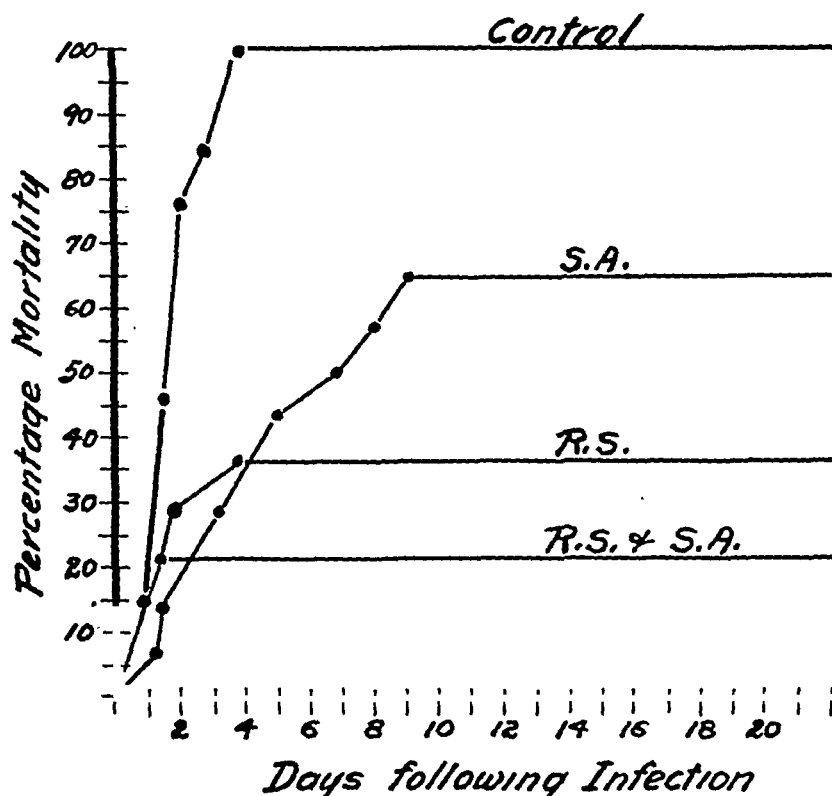


FIG. 2.—MORTALITY CURVES OF RATS INFECTED WITH APPROXIMATELY 10 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 12 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of 10^{-5} broth dilution of an 18-hour broth culture intracranially.
Treatment: Controls: 13 rats, no treatment. S. A.: 14 rats, 100 mg. of sulphanilamide twice daily for 3 days and once daily for 3 following days. R. S.: 14 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 3 successive days. R. S. and S. A.: 14 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

with sulphanilamide, a third group of 14 was given rabbit serum, and the remaining 14 rats were treated with a combination of rabbit serum and sulphanilamide. The first treatments in each group were given 12 hours following infection. The rabbit serum was given intraperitoneally in 3 equal doses on 3 successive days to a total of 1000 units. Sulphanilamide was administered orally in 100 mg. doses twice daily the first 3 days and once daily for 3 more days.

Results. A graphic representation of the results is given in Figure 2.

All of the 13 untreated animals were dead in less than 4 days. The sulphanilamide group suffered a 64.3% mortality, while in the rabbit serum group only 35.7% died and in the combination treatment group only 21.4% succumbed.

III. Infection with approximately 100 fatal doses and initial treatment delayed 7 hours following infection:

A series of 84 rats was infected as in the two preceding series except that the inoculum was 10 times more concentrated (10^{-4}). Cultures of the blood and distal lumbar portion of the spinal cord of 6 of these rats which were sacrificed in pairs 2, 4, and 6 hours following infection were positive even in the 2-hour animals.

Treatments were begun 7 hours following infection. Sulphanilamide was administered orally to 21 of the rats in 100-mg. doses twice daily for 2 days and once a day for 2 more days. A second group of 21 animals was given rabbit serum intraperitoneally to a total of 1665 units per rat in 5 equal doses distributed over as many days. A third group of 21 rats was given a combination of these 2 treatments, while the remaining 15 animals served as untreated controls.

Results. All of the rats in the control group as well as in the sulphanilamide group died with insignificant differences in survival time. In the serum group, the mortality rate was 81%, while in the combination group only 57% died. A graphic representation of these results is shown in Figure 3.

Pathologic Changes in Brain and Cord. The surviving rats were killed 3 to 6 weeks after infection. Although grossly no recognizable changes were found, microscopically practically all rats showed a diffuse thickening of the brain pia associated with a scanty round cell infiltration. In addition, many animals showed deep cortical scars, foci of calcification, and hemosiderin deposits. The spinal cords showed little or no change. Only a few of the cords showed pial changes corresponding to those seen in the brain. These findings will be reported in detail in a subsequent publication.

Discussion. Under normal conditions antibodies present in the blood do not find their way into the spinal fluid, but in the presence of certain inflammatory changes a limited amount of immune substances may pass the barrier recognized to exist between the blood and the cerebrospinal fluid.^{2,20} Sulphanilamide, on the other hand, is present in the cerebrospinal fluid in concentrations parallel to, but slightly less than, those of the blood in both health and disease.^{2,18a,b,25} It appears probable that the past ineffectiveness of therapy in clinical pneumococcic meningitis may be due in part to the barrier which prevents antibodies injected into the blood stream from attaining effective concentrations in the spinal fluid. A second important factor is the viscid character of the exudate which favors blocks and

hinders a uniform distribution of intrathecally administered serum. Stewart^{26a,b} working with pneumococcic meningitis of dogs found that dye injected over one cerebral hemisphere did not stain the other, and that it was necessary to bring antiserum (and optochin) into intimate contact with the exudate containing the microorganisms in order to obtain therapeutic results. In apparent opposition to this concept is the stand taken by Hoyne¹³, who found intravenous

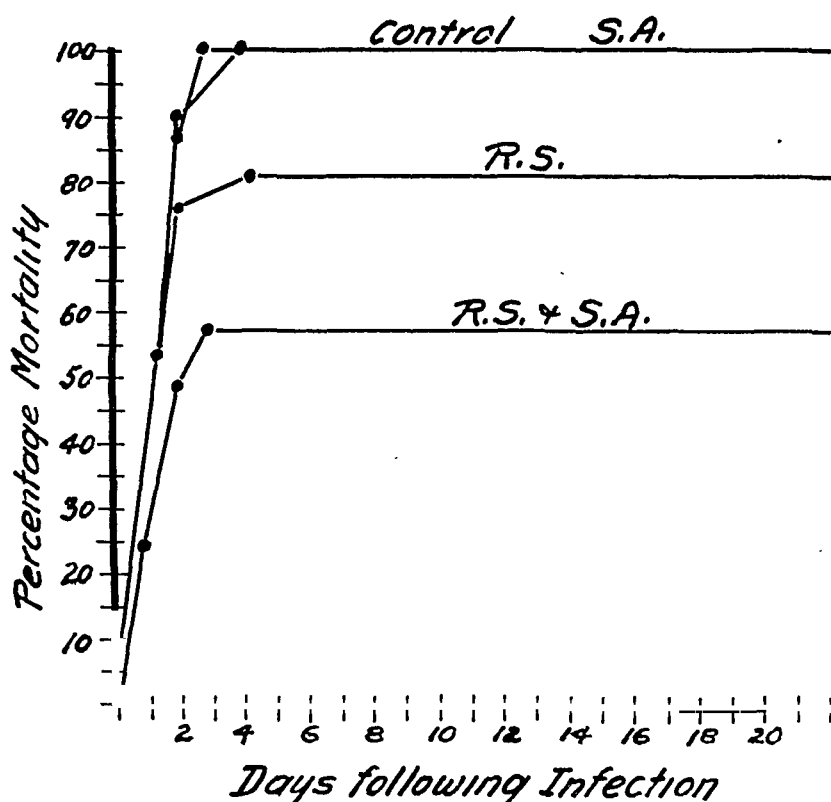


FIG. 3.—MORTALITY CURVES OF RATS INFECTED WITH APPROXIMATELY 100 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 7 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of a 10^{-4} broth dilution of an 18-hour broth culture intracranially. *Treatment:* Controls: 15 rats, no treatment. S. A.: 21 rats, 100 mg. of sulphanilamide orally twice daily and once daily for 2 following days. R. S.: 21 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 5 successive days. R. S. and S. A.: 21 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

serum therapy effective in meningococcic meningitis. The latter disease, however, is considered by some to be primarily a bacteremia with meningitis as a complication.

The remarkable therapeutic success obtained in our experiments with specific antiserum administered intraperitoneally suggests that the so-called cerebrospinal barrier is very permeable to certain Type I antibodies in rats suffering from pneumococcic meningitis. There is

a possibility that this phenomenon may be a function of the effective size of the antibody molecule.^{8,12*} This assumption may explain the superiority of rabbit serum over horse serum (Fig. 1) in spite of the apparently equal dosage.

Comparative results with sulphanilamide and specific serum therapy in experimental pneumococcic pneumonia^{5b,9b} have indicated that sulphanilamide was at least as effective as serum therapy. The fact that the present results do not support our previous findings with horse antiserum may be due to differences inherent in the diseases, or the sera used, or to the fact that a 33% larger dose (based on a human adult dose of 350,000 units) was employed in the meningitis experiments. Although this superiority of horse antiserum over sulphanilamide was negligible, the rabbit antiserum was definitely more efficacious in all experiments.

The best results in each experiment were obtained by a combination therapy of rabbit serum given intraperitoneally and sulphanilamide by mouth. These findings are in complete harmony with conclusions previously drawn by us^{5b,9b} and by Branham and Rosenthal⁴ and they support the rationale of similar clinical procedures.⁷

Conclusions. 1. An experimental meningitis due to a virulent Type I pneumococcus has been produced in rats.

2. Sulphanilamide by mouth and antipneumococcic sera given intraperitoneally, were both effective in reducing the mortality of experimental pneumococcic meningitis in rats.

3. A combination of sulphanilamide by mouth and specific serum intraperitoneally was the most effective treatment, and showed a marked therapeutic effect even in the presence of an overwhelming infection.

4. Sulphanilamide therapy proved practically as effective as horse antipneumococcic serum therapy. Rabbit antipneumococcic serum was more effective than similar horse serum.

5. Delay in treatment or massive increase in the size of the infecting dose diminished the percentage of recovery irrespective of the treatments attempted.

* Another possible explanation, that of species differences, is ruled out by our more recent work with Type III pneumococcic meningitis in rats in which specific rabbit antiserum was completely ineffective. This work will soon be published.

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CONGO RED: TOXICITY AND SYSTEMIC ACTIONS.

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THE increasing importance of Congo red as a diagnostic and therapeutic agent indicates the desirability of acquiring accurate information regarding its toxicity and general actions. Recent uses of the dye as a hemostatic¹¹ in pernicious anemia,^{7,9} in infections,¹ and in experimental intoxications³ indicate unusually diverse and interesting effects possessed by one substance. Therefore, it was thought desirable to supplement the present meager and incomplete pharmacological data on this dye with more detailed information. It is hoped that this will serve as a basis for the study of other interesting dyes of the same general group. This paper discusses the toxicity, fatal doses, cause of death and muscular actions in different animals.

Methods. The dye used was that marketed under the designation "Congo red 4B" (Coleman and Bell). Unless otherwise stated, the solution for injection was always prepared by dissolving 1% Congo red in a 5% aqueous solution of dextrose. The solution was boiled and then filtered through fine filter paper. When this solution was kept in a refrigerator, it maintained its colloidal properties and clear appearance almost indefinitely. On the other hand, Congo red in normal saline solution (0.85% NaCl) seldom remained stable longer than 12 to 24 hours due to a "salting out" effect of the sodium chloride. Some have used the Congo red dissolved in distilled water, but this is undesirable for parenteral administration because the solution is hypotonic.

Toxicity and Fatal Doses. The available data on the toxicity of Congo red are so limited^{5,6,8,11} that it is difficult to draw accurate conclusions as to tolerated or fatal doses. We have extended the

data on a great number and variety of animals, *i. e.*, 249 pigeons, rabbits, rats and cats. The results should be helpful in obtaining an idea of the order of toxicity for humans. All injections were made intravenously.

The general symptoms of toxicity were similar in all species, except pigeons, which reacted rather rapidly and sometimes with convulsions. Immediately following the injection of a fatal dose of Congo red, the animals became depressed, and moved about the cage only when stimulated. Within a period of 1 to 24 hours, and depending on the species and dose, the depression passed into coma, and death supervened promptly. Respiration was practically unchanged until just before death, when periodic hypernea and apnea often occurred.

At autopsy, the blood was always fluid and did not clot after standing several hours. The heart was widely dilated, especially the ventricles. The lungs were congested, and occasionally there were subpleural hemorrhages. Histologically, there was widespread dilatation of capillaries, arterioles and venules; the hyperemia was especially marked in the kidneys and lungs, but to a less extent in the heart and liver. The lungs also showed occasional areas of extravasated blood.

The per cent mortalities according to varying doses of Congo red in different species are presented in Table 1. The highest tolerated single doses in mg. per kg. body weight were as follows: pigeons, 100; rats, 140; rabbits, 200; cats, 100. The doses causing 50% mortality in mg. per kg. were as follows: pigeons, 150; rats, 190; rabbits, 250; cats, 125. These doses were from 25 to 90% greater than the tolerated doses in the same species.

The results show considerable variation between species, thus making it difficult to predict the tolerance of the dye in humans. The highest reported single dose of the dye used clinically is 150 mg. or 2.5 mg. per kg. for a 60-kg. adult. This is only one-fortieth the maximum tolerated dose in pigeons and cats, the most susceptible species. Therefore, it would appear that the margin of safety in using Congo red intravenously is rather wide.

The absorption from intramuscular, subcutaneous and intraperitoneal injections in rabbits and pigeons was too slow and incomplete to give reliable results for toxicity. The absorption is to be described separately. Macht and Grumbein⁶ have reported intraperitoneal fatal doses of about 200 to 400 mg. per kg. for mice, and death in these animals after subcutaneous injections for several days. Matsuo⁸ reports the following unusually high fatal doses: frog, 2 mg. per gm. (lymph sac), and mouse, 1.5 mg. per gm. (method of administration not stated).

Toxicity According to Solvent. Since Congo red is often used clinically in purely aqueous or normal saline solutions, it was interesting to compare the toxicity of such solutions with Congo

red in 5% dextrose solution. Of 10 pigeons, injected with 160 mg. per kg., Congo red in distilled water, 5 died (mortality, 50%), whereas 8 of 10 other pigeons died (mortality, 80%) injected with 160 mg. per kg. in normal saline solution. The mortality results showed also that Congo red in distilled water was about as toxic as the dye in dextrose solution (Table 1), while Congo red in saline solution was more toxic. The higher toxicity of saline solutions is attributed to the flocculation of Congo red which occurs promptly in Congo red saline mixtures. Such flocculated solutions are obviously undesirable, if not dangerous, for intravenous injection in humans. Except when indicated, the following experiments were made with Congo red in 5% dextrose solution.

TABLE 1.—INTRAVENOUS TOXICITY OF CONGO RED.*

Dose, mg. per kg.	Pigeons.		Rats.		Rabbits.		Cats.	
	No.	Died, %.	No.	Died, %.	No.	Died, %.	No.	Died, %.
50	7	0
100 . . .	6	0	8	0	3	33
120 . . .	11	18						
140 . . .	22	27	20	0				
150	3	66
160 . . .	23	48	20	15				
180 . . .	22	77	20	20				
200 . . .	7	100	20	70	2	0	1	100
220	20	85				
230	5	100	8	25		
250	8	62	1	100
275	5	80		
300	4	75		
350	3	100		

* One per cent dye in 5% dextrose solution.

Repeated Intravenous Injections. Six rabbits were injected daily by vein with from 25 to 50 mg. per kg. Congo red for 7 to 14 days. No ill-effects were observed in any of the animals, nor was there any loss of body weight. Four pigeons were given 4 daily intravenous injections of 50 mg. per kg. each, or a total of 200 mg. per kg. of pigeon, without demonstrable effects. Three of the rabbits used received 50 mg. per kg., for 14 days, or a total of 700 mg. per kg. This would correspond to a total of 42 gm. for a 60-kilo man, which is much greater than the doses proposed thus far. Accordingly, there are few therapeutic agents which have such a large margin of safety as Congo red used intravenously. However, large single and repeated small doses cause marked disturbances of the circulation which may result in death.

Cause of Death from Intravenous Injections. The cause of death from Congo red used intravenously was studied in 10 rabbits and 13 cats. The rabbits were anesthetized with 30 mg. pentobarbital per kg. intraperitoneally, and the cats, with 1.5 gm. urethane per kg. gastrically. Blood pressure was recorded from a mercury manometer joined to a carotid artery; respiration was recorded with a

to the zero level. As the pressure approached zero, the pulse slowed down and finally ventricular contractions stopped altogether. Respiration was not changed either as to rate or depth, until the blood pressure reached shock level. At this point, alternate periods of apnea and hypernea often occurred. Respiration never stopped completely until the blood pressure had fallen to the zero level.

During the phase of rising blood pressure, the liver, intestine and leg all showed some increases in volume. The venous pressure rose slightly and the heart dilated, usually with a coincident increase in amplitude of contractions. As the blood pressure began to fall the venous pressure suddenly rose, the liver and intestine continued to increase in volume, but the leg diminished in size. The amplitude of the cardiac contractions became smaller, with a marked diastolic tendency. When the blood pressure fell below the shock level, the liver and intestine usually decreased slightly in volume and the venous pressure fell.

These phenomena are consistent with circulatory collapse, probably due to direct cardiac depression by the dye. As a result, the blood is dammed back in the venous system, thus causing passive congestion of the lungs, liver and intestines. The leg becomes passively constricted because of diminished cardiac output of blood into the periphery. These phenomena and duration of life are not affected by artificial respiration begun before the injection and continued throughout the experiment. Atropine has no effect on the terminal slowing of the heart, thus indicating that the depressant action of the dye is direct on the cardiac muscle and not of reflex vagus origin. When the blood pressure has fallen to the shock level, epinephrine, in large doses, produces a small and typical, though fleeting, rise in blood pressure, which is further evidence of the cardiac depression. That death from single fatal doses of Congo red is not due to the volume of fluid injected was shown by the fact that the injection of equal volumes of isotonic dextrose solution produced only slight rises in pressure. The results with such an "inert" solution resemble closely those of the initial action of Congo red. That is, with the slight arterial pressor effect the venous pressure rises slightly and there are slight increases in size of the leg, liver and intestines, with a slight diastolic distention of the heart. Complete recovery from Congo red occurs in 15 to 20 minutes. The initial results are plainly fluid-volume effects plus some colloid effects which, however, are not comparable with those of blood transfusion, or of acacia under favorable conditions.

Repeated Small Doses. Up to 4 successive intravenous injections of 50-mg. doses of Congo red per kg. were given. These were alternated with injections of equal volumes of 5% dextrose (or 6% acacia) solution, in order to compare the effects of the colloidal dye with a comparatively inert crystalloid and a colloid, as controls. Injection of the first dose of 50 mg. Congo red produced no greater

effect than the control solutions, but the second or third injection produced a profound, though fleeting, depression of the circulation (Fig. 1). This depression occurred when a total of 100 to 150 mg. per kg. of the dye had been injected, an amount close to a fatal dose. This depression lasted about 5 minutes, and the organ changes were similar in all respects to those from a single large fatal dose. After 4 injections of Congo red, or a total of 200 mg. per kg., had been given, further injections of the dye had practically no more effect than dextrose or acacia alone. However, by this time, the blood pressure had fallen steadily, and the animal died finally from cardiac paralysis as from a single fatal dose. In view of this apparent cardiac poisoning in the intact mammal, it was interesting to observe the effects of the dye directly on cardiac muscle of perfused and excised strips.

Effects on Cardiac Muscle. Experiments were made with perfused turtle and frog hearts and excised strips of rabbit auricle. Six turtle hearts were perfused *in situ* according to Greene's method, using the dye in turtle heart—Ringer's solution.¹⁰ The output was recorded by an automatic bucket recorder. Contractions were recorded with a lever attached to the frenulum at the apex of the ventricle. After a satisfactory control record, Congo red in concentrations of from 1 to 40,000 to 1 to 1000 was added to the perfusion fluid.

All hearts showed a prompt systolic tendency (Fig. 2), the contractions became smaller, and the flow decreased or stopped. With higher concentrations, the ventricles stopped in systole, but the auricles continued to beat feebly. After repeated perfusion of the dye, the heart became less sensitive and, in some cases, responded only to high concentrations. The marked systolic contraction was partly relieved by perfusion with quinidine or excess potassium, but atropine had no effect, thus indicating that the systolic action was the result of a stimulation of this cardiac muscle.

Six frog ventricles were perfused according to Straub's method. After a satisfactory control period, perfusion fluid containing Congo red in concentrations of from 1 to 20,000 to 1 to 200 in frog Ringer's solution was added to the cannula. Under these conditions, the frog ventricles responded quite differently from the turtle hearts, for in only 2 ventricles was systolic standstill obtained. The typical response may be seen in Figure 2, which shows a transient period of stimulation, during which the amplitude of contractions was increased, followed by a progressively increasing depression, the heart stopping in diastole. The entire course of events required 15 to 35 minutes, depending on the concentration of Congo red. In 2 cases, the ventricle stopped in systole, but after a few minutes relaxed and remained dilated. The rate was usually not affected until just before stoppage, when the contractions slowed down rapidly.

Three experiments were made with excised strips of rabbit auricle. The rabbits were killed by bleeding, and the hearts removed immediately after death. Strips of the auricle were attached to a light heart lever and immersed in a bath containing 10% blood in oxygenated Locke's solution. After a control period, Congo red in a concentration of 1 to 1000 was added. Within a few minutes the contractions became smaller and the general tone of the strip increased. The rate was practically unchanged (Fig. 2). When the Congo red solution was replaced with fresh Locke's solution, the strip recovered partially from the stimulation. As with turtle hearts, repeated application of Congo red to frog ventricles produced a refractory state so that very high concentrations of the dye were necessary to produce demonstrable effects.

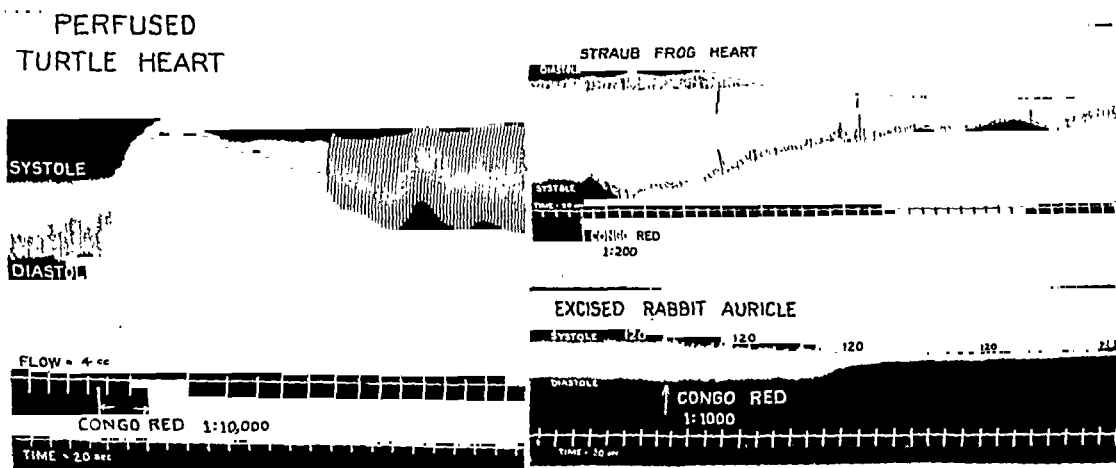


FIG. 2.—Effects of Congo red on perfused turtle heart and isolated frog ventricle and rabbit auricle.

The results obtained on isolated amphibian and mammalian cardiac muscles indicate that Congo red tends to stimulate this type of muscle. This seems to be true for the more stable turtle and rabbit hearts than for the less stable frog hearts, although the latter showed evidences of stimulation in the majority even though sometimes fleeting. Although a digitaloid action has been claimed for some dyes, and the results obtained by us resemble such action, our analysis was not sufficient to justify comparisons along this line. The stimulation of the isolated heart does not, of course, agree with the depression of the heart *in situ*, but the usage of Congo red was not comparable. That is, the dye was used in saline solutions on the isolated heart and such solutions lose their colloidal properties, whereas in the intact circulation the colloidal properties are probably preserved. While the relationship of the physical state of the dye to cardiac function is not understood, this should not be overlooked in determining the fundamental nature of the pharmaco-

dynamic action of the dye. Unfortunately, circumstances did not permit us to continue with this part of the work at this time. The tonifying action on cardiac muscle is worthy of further study as it was found also on smooth muscles.

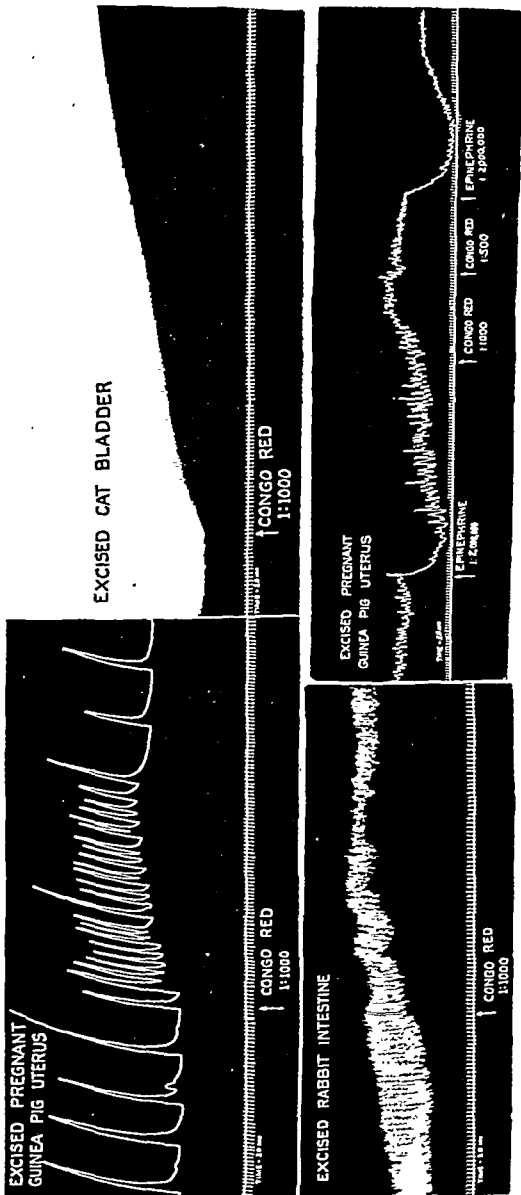


FIG. 3.—Congo red on excised organs.

Excised Smooth Muscles. Congo red has been reported to produce a tonifying action on smooth muscle, particularly on excised intestine.^{2,12} We have tested the effects of the dye on other smooth muscles and confirmed that the stimulation is general, and direct

on the muscle. Results were obtained with uterus, intestine and bladder of cats, guinea pigs and rabbits. Oxygenated Tyrode's solution was used throughout. From 17 to 26 tests were made on all organs obtained from at least 3 different animals of each species. The following concentrations of the dye were used on the different organs: bladder, 1 to 1000 to 1 to 500; pregnant and non-pregnant uterus, 1 to 2000 to 1 to 250, and intestine, 1 to 5000 to 1 to 500. The reactions of all these organ strips were characterized by an increase in tone and a decrease in amplitude of contractions. On the whole, Congo red in 5% dextrose solution caused more pronounced effects than in Tyrode's solution. The typical effects of the following autonomic drugs were produced on all organs after treatment of the organ with, or in the presence of, Congo red: barium, epinephrine and nitrite. Acetylcholine and nicotine were still effective on intestine. The reactions of intestines to post-pituitary solution were often, though not consistently, decreased after the addition of the dye to the organ. Using the dye in whole plasma, or in 10% blood in Tyrode's solution, produced smaller stimulant reactions in the organs. Previous atropinization and nicotization of the bladder and intestine and ergotoxinization of augmentor types of uteri did not prevent the tonifying action of the dye. Illustrations of typical reactions of the different organs to the dye and to autonomic drugs are presented in Figure 3.

According to the results obtained, Congo red is a direct smooth muscle stimulant for isolated intestinal and urogenital organs, independently of innervation, but in the presence of blood colloid elements this stimulation is appreciably reduced. The typical reactions to autonomic muscle-nerve poisons are preserved in the dyed organs. Our results with drugs on excised intestinal muscle confirm those of Ishigami.⁴ The results of several investigators leave doubt that Congo red can excite the motor activity of cardiac and smooth muscles, but how this excitation is produced is not understood. Whether the dye acts similarly on skeletal muscle is not known, although Ishigami claims that the irritability of skeletal muscle and nerve of frogs is not affected. However, it is well known that the dye can protect skeletal muscle and nerve from the paralytic action of curare. The protective action of Congo red can be extended to a variety of cellular and tissue functions, a phenomenon to be described in another paper.

Conclusions. 1. The intravenous fatal dose of Congo red in pigeons, rats, rabbits and cats varies from about 150 to 250 mg. per kg. for over 60% of the animals. The comparatively small doses used in therapeutic and diagnostic practices indicate a wide margin of safety in the use of the dye intravenously.

2. The toxic symptoms are characterized by general depression and collapse. The dye is less toxic in dextrose than in saline

solutions. The cause of death from Congo red is circulatory collapse, as a result of direct cardiac depression.

3. Cardiac muscles of the perfused turtle heart and frog ventricle and excised rabbit auricle are generally directly stimulated by Congo red as indicated by an increase in tone, and stoppage of the heart in systole; frog ventricle showing variations in reaction.

4. Congo red stimulates directly the smooth muscles in isolated bladder, pregnant and non-pregnant uterus, and intestine, by a direct action on the smooth muscle. Reactions of these organs to autonomic drugs are not changed by the dye.

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CONGO RED: ABSORPTION, DISTRIBUTION AND SOJOURN IN BLOOD.

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CONGO red has been used intramuscularly and intraperitoneally in therapeutics without substantial proof of adequate absorption by these routes.^{4,9} Since many systemic effects of the dye probably depend on an adequate concentration in the blood, information on the content and sojourn of the dye in the circulation is of utmost importance, including knowledge of its distribution in the tissues and fate in the body. This paper presents data obtained from animals bearing on these questions.

Estimation of Congo Red in Blood and Tissues. The concentration of Congo red in plasma can be determined by direct comparison with solutions of the dye of known strength, but this method is unreliable for blood, or in the presence of hemolysis and unsatisfactory for tissues. Some time was spent in working out a procedure which could be applied to blood and tissues. Precipitation of the proteins with trichloroacetic acid, tungstate, heat and so on was tried, but discarded because the Congo red was removed with the cellular constituents. Preliminary digestion of the protein material with pepsin and pancreatin did not result in a satisfactory recovery

of the dye. Extracting with alcohol³ gave better results, but with some tissues, particularly liver, recovery was poor. Extraction with acetone, according to Taran,⁷ yielded the best results.

The following procedure was finally adopted: The sample of tissue was cut into small pieces and ground in a mortar with a small amount of sand and water until an even mash was produced. Two volumes of acetone were mixed with 1 volume of tissue mash, shaken, and allowed to stand for 1 to 2 minutes. The mixture was then filtered through medium filter paper. Such treatment gave a clear colorless filtrate with all blank (undyed) tissues, except liver which sometimes gave a slight yellowish color. Bile and urine and pigeon blood also gave yellowish filtrates, which concealed low concentrations of Congo red. The acetone extract was compared directly with permanent known solutions of the dye as standards, which were diluted so that results could be read directly. The method was checked with Congo red added to blood and tissues in concentrations of from 1 to 1000 to 1 to 100,000. The total dye recovered was from 95 to 100%, from all concentrations to 1 to 50,000. With liver and urine, recovery at this concentration was only about 50%. About 75% Congo red could be recovered from blood and most tissues containing added concentrations of 1 to 100,000.

Absorption and Sojourn in Blood. The systemic absorption of Congo red after intramuscular, intravenous and intraperitoneal injections was determined by the level of the dye in the bloods of rabbits and pigeons at different periods following the administration of 1% Congo red in 5% dextrose solution. Blood was withdrawn by cardiac puncture at intervals of 4 minutes, 1 hour and 4, 8, 12 and 24 hours, after injection. It was put directly into 2 volumes of acetone, and the Congo red determined according to the method outlined.

TABLE 1.—AVERAGE CONGO RED CONTENT OF BLOOD ACCORDING TO DIFFERENT METHODS OF ADMINISTRATION.

Time.	Pigeons (75 mg. per kg.).			Rabbits (100 mg. per kg.).		
	Intra-muscular, mg. %.	Intra-peritoneal, mg. %.	Intra-venous, mg. %.	Intra-muscular, mg. %.	Intra-peritoneal, mg. %.	Intra-venous, mg. %.
4 min. . .	0.0	6.25	125.0	0.0	0.0	160.0
1 hour . .	0.3	7.40	55.5	1.6	16.0	128.0
4 hours . .	=	4.70	17.9	2.1	25.0	69.0
8 hours . .	0.0	3.20	8.9	2.0	22.0	42.0
12 hours . .	0.0	1.80	3.0	1.3	13.0	16.0
24 hours . .	0.0	0.85	0.6	1.0	1.0	0.2

The results obtained on 9 rabbits, injected with 100 mg. per kg. Congo red, 3 each intramuscularly, intraperitoneally and intravenously, are presented in Table 1. The concentrations after intravenous injections agree closely with those obtained in man by Bennhold,¹ who reported a 20% removal of the dye during the first hour; only a trace remaining at the end of 24 hours. The intramuscular and intraperitoneal injections gave poor results, since the peak of absorption in each group occurred in about 4 hours, and the blood concentration after intraperitoneal injections was only one-

third that obtained after the intravenous, in a corresponding period. At no time did intramuscular administration result in the magnitude of systemic absorption achieved with intravenous and intraperitoneal injections; it was only about one-tenth to one-thirtieth the content at certain intervals.

The results on 18 pigeons each injected with 75 mg. Congo red per kg. were similar to those on rabbits; 3 groups of 6 pigeons each were injected intramuscularly, intraperitoneally and intravenously. About the only difference from rabbits was a more rapid disappearance of the dye from the blood, nearly 50% being removed at the end of the 1 hour after intravenous injection. For the same reason, the intramuscular and intraperitoneal injections never gave blood concentrations equal to those of intravenous injections.

The poor results on systemic absorption of Congo red obtained with administrations other than intravenous are not surprising considering the physical properties of the dye. For it is well known that colloidal substances are poorly absorbed from the muscles and the peritoneum. Obviously, therefore, when the systemic actions of Congo red are dependent upon a high level of dye in the circulation, the only acceptable method of administering it is the intravenous. Furthermore, where a prolonged action is desired, as in pernicious anemia, experimental intoxications, and infections, the dye must be administered repeatedly in order to insure a continuous systemic action. According to results in animals treated with high and extra therapeutic doses, the dye content of the blood approaches a level of inefficiency by the end of 12 hours and is practically absent at the end of 24 hours, regardless of the method of administration. Smaller and therapeutic doses would possibly require injections as often as every 4 hours, but this suggestion should be tested in case of human medication.

Distribution of Congo Red in Tissues. It has been suggested that Congo red is removed from blood chiefly by the reticulo-endothelial cells and the rate of removal is a measure of the functional efficiency of this system.^{2,6,10} If this hypothesis is correct, Congo red should be distributed according to the richness of organs in reticulo-endothelial cells. The results obtained by me do not sustain this. On the contrary, the Congo red is distributed fairly evenly in the extracellular tissue fluids of the body.

Ten rabbits and 4 cats were injected intravenously with 1% Congo red in 5% dextrose solution, using doses of from 50 to 450 mg. per kg. Tissues were removed 1, 24 and 72 hours later. No effort was made to wash out all the blood. The results obtained are shown in Table 2, grouped according to time of tissue removal after injection, so that animals with a high blood content of the dye could be compared with those with a low blood content.

It is seen that 1 hour after ingestion of doses from 50 to 450 mg. per kg. the Congo red was chiefly in the blood and those organs

with rich capillary beds. Apparently, anesthesia and nerve paralysis had no influence on the distribution of the dye, except for quantitative differences due to the different doses used. The cats had been used for toxicity studies of the dye and were urethanized, atropinized and curarized.⁵ The high blood content was not surprising in view of the colloidal nature of the dye. Interestingly, the lungs contained the highest concentration of all the tissues examined. This was particularly true of cats receiving the fatal doses. Kidney, liver and pancreas were next highest, and then came the heart and spleen. Striated muscle and brain invariably contained the least amount of dye. Bile from the gall bladder contained about as much as liver, while urine contained an undetermined amount despite the high renal concentration of the dye.

TABLE 2.—DISTRIBUTION OF CONGO RED IN TISSUES OF RABBITS AND CATS.

Time after injection	One hour.		Twenty-four hours.			Seventy-two hours.
Total dye injected, mg. per kg.	50	450*	50	100	700†	275
Number of animals	2	4	2	2	2	2
	Mg. %.	Mg. %.	Mg. %.	Mg. %.	Mg. %.	Mg. %.
Blood	43.5	568.0	0.00	0.5	0.57	0.57
Brain	0.48	4.9	0.00	0.0	0.30	0.55
Muscle	0.37	3.8	0.00	0.41	0.36	1.77
Skin	1.6	..	0.56	..	3.2	2.6
Heart	18.4	..	0.22	..	3.1	5.38
Spleen	2.9	279.0	1.72	..	7.9	91.0
Pancreas	210.0
Liver	18.2	197.0	2.5	15.6	41.2	62.7
Lung	23.5	434.0	1.9	5.7	15.7	27.2
Kidney	22.9	228.0	28.6	49.9	105.7	104.8
Bile	21.6	..	146.0	..	162.0	59.5
Urine	(+)	(-)	(-)	..	3.1	(-)

* This group consisted of cats, anesthetized with 1.5 gm. urethane per kg.; all other animals were rabbits.

† Daily dose of 50 mg. per kg. for 14 days.

The blood was nearly free of the dye 24 hours after injection of doses of 50 to 100 mg. per kg. in 4 rabbits and 50 mg. daily for 14 days (total 700 mg. per kg) in 2 other rabbits. The tissues gave values which varied only quantitatively. The concentration of the dye in the tissues could not be attributed to the blood content of the dye, since the blood was practically free of the dye. Blood, brain and striated muscle of all animals contained about equal, although the lowest, concentrations of dye. Skin and heart muscle contained appreciably larger amounts, while spleen, lung, liver and kidney, in this order, contained increasing amounts. The kidneys always contained twice as much as any other tissue. Bile from the gall bladder generally contained very large quantities, while urine contained only small amounts of the dye, if any. The comparative absence of the dye in urine was surprising in view of the high renal

content. Since the Congo red was not readily released from the kidneys, these organs presumably possess a selective retention for it.

The high retention of the dye in the kidneys was evident also in the 2 rabbits which had been given 275 mg. per kg. At this time, the concentration in the bile had fallen to about one-third that at the end of 24 hours. While the biliary channels are the main paths for excretion of the dye, the kidneys, by contrast, held relatively much more. The remaining tissues contained about the same amounts as at 24 hours. For instance, the blood content was practically the same. In other words, there appears to be a delayed removal from the system after 24 hours of sojourn in the body.

Many of the tissues were examined histologically in an attempt to locate the Congo red in the cells, but only in the kidneys was it possible to identify the dye. In these organs, the dye was present chiefly in the cells of the tubules, where it had a granular appearance. The entire protoplasm and extracellular spaces were definitely stained a diffuse red color. Most of the glomeruli remained uncolored. The nuclei of the cells were comparatively free of the dye.

It is clear from these results that, even as late as 72 hours after intravenous injection, when the greater part of the dye has long been removed from the blood stream, Congo red is distributed systemically without demonstrable relationship to the reticulo-endothelial system. Accordingly, the use of Congo red as a functional test for this system is based on a false hypothesis. With the exception of the high concentration in the kidney tubules, Congo red tends to be distributed evenly in those organs having a high extracellular tissue fluid. The organs, which Wallace and Brodie⁸ reported taking up large quantities of iodide and thiocyanate, are the same organs which take up large quantities of Congo red. However, the data obtained by me would seem to indicate that the Congo red in the liver, spleen, lungs, kidneys, skin and so on is partially bound, physically or chemically, by some cellular or non-cellular constituent, otherwise its concentration would remain in equilibrium with that of the blood. Proteins are apparently not concerned, since the dye escapes fairly readily from the blood. It is conceivable that tissue fluid or lymph may contain some substance like amyloid, or its precursor, which has a strong affinity for Congo red, and that, in the condition known as amyloidosis, this substance is merely increased. Further study of this phenomenon was not attempted at this time.

Conclusions. 1. Intramuscular and intraperitoneal injections of Congo red in pigeons and rabbits failed to produce concentrations of the dye in the blood comparable to intravenous injections.

2. Injected intravenously, Congo red disappears from the blood stream at a constant rate, only traces of the dye remaining at the end of 24 and 72 hours, even after large doses.

3. After disappearance from the circulation, most of the Congo red is distributed to those organs possessing large amounts of extra-cellular tissue fluid, and is presumably loosely bound in some way to some substance or structure in tissue fluid.

4. The kidneys of cats and rabbits possess a rather high selective retention for Congo red, but the biliary passages are the main channels for excretion of the dye.

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CONGO RED: HEMATOLOGIC ACTIONS.

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SOME of the most interesting though controversial effects of Congo red are those on blood. Despite many clinical reports of its usefulness in treatment of pernicious anemia and hemorrhages, there have been few controlled studies of its effects on hemolysis, cell counts, suspension stability, coagulation and bleeding time.

Antihemolytic Action. That Congo red may, under certain conditions, cause remissions in pernicious anemia supports the opinion of Dock,¹ among others, that this blood disease is fundamentally a hemolytic anemia. A protective action of the dye for the fragile erythrocytes, *i. e.*, an antihemolytic action, might be the basis of the beneficial effects of Congo red in pernicious anemia. The following experiments were made to test the possible antihemolytic actions of this colloidal dye in various *in vitro* hemolytic systems. Whole human blood from healthy males was added to each hemolytic system, the final concentration of red cells being 1%. Changes in hemolysis were determined by counting the cells in a hemocytometer chamber. The results were recorded in per cent hemolysis of the original concentration of blood. The results obtained are presented as curves in Figure 1.

Hypotonic Sodium Chloride Solution. Tests of fragility in hypotonic sodium chloride solution containing the dye were made as follows: 2.7 cc. of sodium chloride solution with salt concentrations of from 0.5 to 0.26% were mixed with 0.3 cc. Congo red solution to make final concentrations of the dye 1 to 4000, 1 to 2000 and

1 to 1000. As controls, the same dilutions of sodium chloride were mixed with 0.3 cc. 5% dextrose solution. After adding the blood, the tubes were shaken and allowed to stand in an incubator at 37° C. for 2 hours. The results of a typical experiment are shown

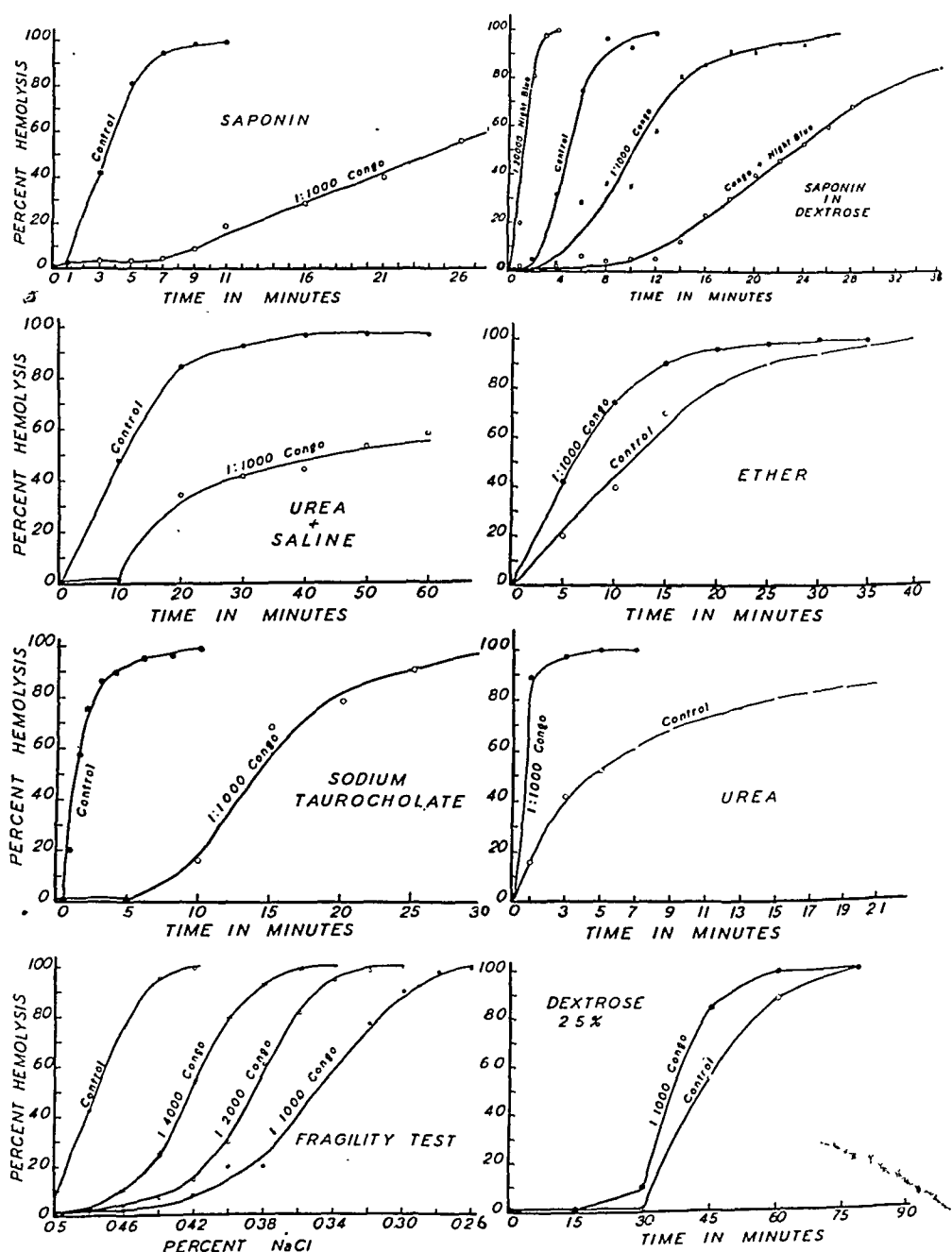


FIG. 1.—Effect of congo red on hemolysis of human blood by different agents.

in the left-hand corner of Figure 1, in which per cent hemolysis is plotted against concentration of salt. A protective action of the Congo red is clearly evident. Whereas, in the control, 50% hemolysis occurred in 0.48% sodium chloride, not so in Congo red. Definitely lower dilutions, *i. e.*, 0.42, 0.39 and 0.35%, were required to produce the same degree of hemolysis when the dye was present in concentrations of 1 to 4000, 1 to 2000 and 1 to 1000, respectively. Essentially the same results were obtained with 3 other samples of blood.

That the degree of inhibition was directly dependent on the concentration of the dye at the time hemolysis was taking place was shown in the following experiment: Whole blood was mixed with Congo red 1 to 1000, and the mixture was allowed to stand for 2 hours. At the end of this time, the resistance of this mixture to hypotonic saline solution was compared with that of a control sample of blood and found to be identical.

Isotonic Dextrose Solution. Since blood mixed with isotonic dextrose solution is rather promptly, though partially, hemolyzed, it was not feasible to test the effect of Congo red on the resistance of red cells to varying hypotonic strengths of this sugar. Instead, the speed of hemolysis in dextrose solutions was determined in the presence and absence of Congo red. One test tube was filled with 2.5% dextrose solution and sufficient Congo red added to make a concentration of 1 to 1000; another tube was filled with 2.5% dextrose solution plus 5% dextrose equal to the volume of dye in the first tube. Blood was added, and both tubes were shaken and put in an incubator at 37° C. The cells remaining in each tube were counted every 5 minutes, and per cent hemolysis plotted against time. The averages of 3 such experiments are shown in the right hand corner of Figure 1. It is seen that Congo red caused a slight, but definite, increase in speed of hemolysis as compared with the control.

Ether. Ether, 7% strength, in 0.9% sodium chloride solution was used as a hemolyzing agent. To one test tube was added ether-saline solution plus Congo red to a final concentration of 1 to 1000, and to another tube ether-saline solution plus 5% dextrose. After the addition of blood, both tubes were stoppered and allowed to stand at room temperature. Cell counts were made every 5 minutes. The averages of 3 experiments, shown in the right upper segment of Figure 1, were similar to those with dextrose, and leave no doubt of a definite increase in speed of hemolysis caused by the dye, as compared with the control.

Hypertonic Urea Solution. As is well known, urea, even in "hypertonic" strength, causes a rapid hemolysis of red cells. A solution of 20% urea in distilled water was used, and 2.7 cc. of this solution was made up to 3 cc. with sufficient Congo red to make a concentration of 1 to 1000, and of 5% dextrose solution for the con-

trols. Blood was added to each tube and red cell counts were made every few minutes. The curves in Figure 1, which show averages of 3 experiments, leave no doubt that Congo red caused rapid and complete hemolysis, while the control untreated blood required about 20 minutes for complete hemolysis. Therefore, the results were similar to, but more striking than, those with dextrose and ether.

Urea in Saline Solution. Since the results with hypotonic saline solution showed a striking protective action of Congo red, but in solutions of dextrose, ether and urea, the effects were just the reverse, it was interesting to consider if the sodium chloride played a part in the protective action. Figure 1 shows the average results of 3 experiments in which 0.5% sodium chloride was added to the 20% solution of urea. Tubes of this solution were prepared without and with Congo red, 1 to 1000, blood was added, both tubes were shaken and then allowed to stand in an incubator at 37° C. Cell counts were made every 10 minutes. The control tube without the dye showed complete hemolysis in about 40 minutes, while tubes containing Congo red, only about 50% hemolysis at the end of 1 hour. Thus, the presence of salt mediated a protective action of the Congo red against hemolysis by urea, and the same was true for taurocholate and saponin.

Sodium Taurocholate in Saline Solution. Sodium taurocholate, 1 to 1000, was tried in 0.9% sodium chloride solution. Hemolysis of red cells in the absence and presence of Congo red, 1 to 1000, in this solution, was observed in 3 experiments. The average results are shown in Figure 1. In the control tube, hemolysis was complete in 5 minutes, while in the presence of Congo red it was not complete until about 30 minutes.

Saponin in Saline and Dextrose Solutions. Saponin, 1 to 20,000, in normal saline solution was tried. Congo red, 1 to 1000, was added to the saponin solution, and as a control, an equal volume of 5% dextrose solution was used. Blood was added, and cell counts were made every few minutes. The averages of 3 experiments in Figure 1 show that Congo red produced a striking inhibitory effect. The cells in the control tube were completely hemolyzed in 7 to 8 minutes, while, in the presence of Congo red, only about 60% of the cells were destroyed in 26 minutes.

A further test of the protective action of Congo red against saponin was made with solutions of the dye in dextrose solution, instead of saline solutions. Saponin, 1 to 7000, in 5% dextrose solution was used and the speed of hemolysis determined in the absence and presence of Congo red, 1 to 1000. The averages of 3 experiments in Figure 1 show that Congo red delayed hemolysis about 25 minutes, while the control tube showed complete hemolysis in 12 minutes.

Nature of the Antihemolytic Mechanism. Since the protective action of Congo red against saponin was enhanced by the presence of salt, experiments were made to determine whether this action could be due to some change produced in the physical state of the colloidal dye. For this purpose, Night Blue, an electropositive dye, was used. This dye was added to the same saponin-dextrose system in a concentration of 1 to 20,000 with the result that the speed of hemolysis was increased (Fig. 1). However, when the Night Blue was combined with the Congo red, a striking protection against saponin-hemolysis was produced (Fig. 1). This result can only be explained by some change in the physical state of the Congo red, which is precipitated by Night Blue as well as by salt. Accordingly, the protective action of Congo red may be due to the formation of a protective film on the surface of the red cells by the precipitated Congo red. Precipitation of this electronegative, emulsoid dye is not as efficient in the presence of sodium chloride as of Night Blue. Therefore, Congo red, in saline solutions, would be expected to give variable, or incomplete protection, as indeed was the case with the different agents tried (Fig. 1).

Congo red shows protection against hemolysis with such a large variety of agents that it appears probable the protection is not due to any specific action on the individual hemolytic agents. In hypotonic sodium chloride solution, the protection could be a salting (precipitating) action on the dye and explained by some film effect on the cells. Therefore, it would be reasonable to expect that the same mechanism would operate in all cases where sodium chloride was present, and this was found to be true generally. With saponin and some of the other agents, the possibility should not be overlooked that the toxic substance may be adsorbed on the surfaces of the dye aggregates and thus might prevent, or render inefficient, a contact with the red cells. However, protection against the hemolysis of saponin in the intact organism could not be demonstrated, but the experimental procedure was not satisfactory. Studies of changes in circulating blood may now be described.

Effects on Blood of Intact Animals. A total of 21 rabbits and 1 cat were used. Congo red was injected in doses of from 10 to 100 mg. per kg. intravenously, as single doses and as daily doses for 1 and 2 weeks. Following the single doses, blood was examined 1 hour, and 3 and 24 hours later, and after repeated doses, 24 hours after the last injection. All procedures for examination of the blood were carried out according to the methods described by Todd and Sanford.⁵ Except for platelet and reticulocyte counts, all bloods were obtained by cardiac puncture. As anticoagulant for the blood, potassium oxalate was used, 10 mg. in 1 cc. of blood. The following results were obtained.

Hemoglobin. This was determined with a Sahli hemoglobinometer. The greatest deviation observed from normal, in any one

animal, was a decrease of 7%, which occurred 24 hours after a single injection of 100 mg. per kg. of the dye. Rabbits receiving 50 mg. per kg. daily for 2 weeks showed no demonstrable changes.

Packed Cell Volume. This also showed little or no change. As with hemoglobin, the greatest change occurred in those rabbits receiving single injections of 100 mg. per kg., and even then there was only an average decrease of 4%.

Red Cell Counts. These followed closely the results on hemoglobin and packed cell volume; no significant changes occurred after single and repeated injections of 25 and 50 mg. per kg. of Congo red. However, 24 hours following 100 mg. per kg., the average count in 2 rabbits fell from 4.4 million to 3.5 million red cells per c.mm. The small decreases in hemoglobin and red cells after large doses of Congo red would be consistent with either destruction or dilution of the blood, but analysis of the phenomenon was not made.

Platelets and Reticulocytes. These elements were determined by the so-called wet method, using brilliant cresyl blue and sodium citrate, the blood being obtained by puncturing a small ear vein. Immediately and for several hours following the injection of 100 mg. per kg. of the dye, the platelets and reticulocytes could not be counted because of agglutination of the red cells about the platelets. The cells were only loosely clumped, since dry smears failed to show this phenomenon. However, the agglutination was indicative of some change in the cell surfaces. Platelet counts, after all doses of Congo red, showed both increases and decreases, which did not average more than 60,000 per c.mm., and were well within the normal range. Reticulocytes showed no change, except in rabbits given 50 mg. per kg. daily for 2 weeks. These continued doses caused a slight reticulocytosis of about 0.7%, probably without significance.

Leukocytes. The counts after 25 mg. per kg. of Congo red, in single and repeated doses, showed no changes. Single injections of 50 or 100 mg., however, increased the white count 4000 to 9000 cells per c.mm. The peak of leukocytosis occurred in 1 to 2 hours, with return to a normal white cell count 20 hours later. The leukocytosis was marked chiefly by an absolute increase in the number of neutrophils.

Sedimentation Rate. This was determined in Cutler tubes of 1-cc. capacity. Because of the normally slow sedimentation rate of rabbit blood, observations had to be made over a period of 3 hours instead of 1 hour, the usual period for other bloods. Single injections of 25 mg. per kg. of the dye increased the sedimentation rate about 80%, while 100 mg. per kg. increased it about 350%. The increase in sedimentation lasted for 48 hours, at least, after a single injection of the Congo red. Hemagglutination, or blood dilution, might be responsible for this change, but it was not studied further.

Blood Coagulation and Bleeding Times. The literature on the effect of Congo red on the clotting time of blood has been reviewed recently by Taliaferro and Haag,⁴ and also by an anonymous writer,³ therefore, it is omitted here. Briefly, most of the reports have been clinical, and unfortunately, not well controlled. The results claimed have been rather striking and to the effect that both phenomena are shortened, thus providing a basis for the alleged hemostatic action of Congo red. The claims seemed worthy of confirmation or refutation and the attempt was made on 21 healthy rabbits.

Bleeding time was determined by transecting a small vein in an ear and noting the time required for the blood flow to stop. As nearly as possible, a vein of the same size was used each time. Coagulation was determined on blood drawn into a syringe directly from the heart and expelled into a small clean test tube. The tube was tipped every 15 to 30 seconds until it could be completely inverted without flow of blood. After suitable control observations on each animal, Congo red was injected intravenously in doses of 10 to 100 mg. per kg. and the coagulation and bleeding times were determined 5 minutes, 1, 3 and 24 hours later. Some rabbits were injected with 25 and 50 mg. per kg. of the Congo red for 1 and 2 weeks, the coagulation time being determined 24 hours after the last injection. Table 1 presents a summary of the results, which were essentially negative.

TABLE 1.—BLOOD COAGULATION AND BLEEDING TIMES IN RABBITS INJECTED WITH CONGO RED INTRAVENOUSLY.*

Dose of Congo red, mg. per kg.	No. of rabbits.	Control.	5 min.	1 hr.	3 hrs.	24 hrs.	36 hrs.	Daily dye for 7 days.	Daily dye for 14 days.
10	5	212 (C) 57 (B)	173 (C) 42 (B)	207 (C) 46 (B)	240 (C) 61 (B)				
25	9	290 (C) 119 (B)	210 (C) 141 (B)	267 (C) 88 (B)	420 (C) 80 (B)	285 (C) 130 (B)	...	315 (C) 132 (B)	345 (C) 110 (B)
50	5	297 (C) 97 (B)	285 (C) 150 (B)	301 (C) 155 (B)	...	215 (C) 112 (B)	285 (C) 135 (B)	405 (C) 135 (B)	365 (C) 80 (B)
100	2	230 (C) 132 (B)	...	1200 (C) 850 (B)	...	242 (C) 227 (B)	265 (C) 157 (B)		

* (C) means coagulation time; (B), bleeding time, each in seconds.

Therefore, these negative results in rabbits, which received extra-therapeutic doses of Congo red, at least for certain disease states, refute the positive claims made for shortening of blood coagulation and bleeding times. Any small tendencies in this direction were well within the range of normal variations and of experimental error. The greatest decreases occurred 5 minutes and 1 hour after 10 and 25 mg. per kg. of the dye and here the maximum shortening amounted to an average of only 25%. With doses of more than 50 mg. per kg., bleeding and coagulation times were prolonged in

all animals. For instance, 100 mg. per kg. increased the coagulation time about 500% at the end of 1 hour, with a return to normal in 24 hours. This effect of large doses of the diazo dyes is well known and has been carefully investigated by Huggett and Rowe.² Of course, the effects of Congo red in clinical pathologic states of the blood might be different from those in healthy rabbits, but the opportunity of investigating clinical conditions was not available to me. At the same time, positive claims have been made for the dye in normal individuals and it has been injected routinely in connection with surgical operations. The character of the evidence to date does not justify its routine use, but further study in pathologic states may be worthwhile.

Conclusions. 1. Congo red in concentrations of 1 to 1000 protects against hemolysis of human erythrocytes by hypotonic saline solution, hypertonic urea and sodium taurocholate in saline solutions and saponin in dextrose and saline solutions. No protective action, but in fact increased hemolysis, occurs with Congo red in hypotonic dextrose solution and in ether and urea in aqueous solutions.

2. The antihemolytic action of Congo red appears to be mediated through a film effect on the cells, as the result of a change in the physical state of the dye, since Night Blue and salt, which increase the flocculation or precipitation of Congo red, also increase its protective action for erythrocytes.

3. Intravenous doses of 10 to 50 mg. per kg. Congo red in rabbits produce no consistent or demonstrable effects on hemoglobin, red blood cells, platelets and reticulocytes. Doses of 100 mg. per kg. produce a slight temporary anemia, with hemagglutination.

4. Single intravenous injections of more than 25 mg. per kg. of Congo red in rabbits cause a moderate leukocytosis, chiefly increases in the number of neutrophils and marked increases in sedimentation rate of blood.

5. Small or large extratherapeutic doses of Congo red in healthy rabbits produce no demonstrable or consistent and sufficient shortening of the blood coagulation and bleeding times, contrary to positive, though uncontrolled, claims in the literature. On the contrary, very large doses of the order of 100 mg. per kg. produce uniform anticoagulating effects.

6. Accordingly, the alleged clinical hemostatic action of Congo red, at least in normal individuals, lacks the support of controlled experimental evidence, but the action might be different in pathologic states.

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BRONCHOGRAPHIC STUDY OF APPARENTLY HEALED LUNG ABSCESES.*

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THE disappearance of the roentgenographic shadows of a lung abscess and its surrounding pneumonitis and the loss of symptoms referable to the abscess are usually accepted as conclusive evidence that the abscess has healed. Reports of the recurrence of lung abscesses,^{1,2,4,5,11} suggest that these criteria of healing are insufficient.

Since the history, the physical examination and ordinary roentgenograms in these cases yield data that are consistent with the idea that healing of the abscess is complete, further investigation of the relationship of the residual condition of the lungs involves the use of bronchography.

Bronchography has been used for many years⁷ in selected cases of pulmonary tuberculosis to determine the effectiveness of thoracoplasties in closing cavities and to demonstrate the presence of bronchiectasis as the source of persistent sputum in the absence of demonstrable pulmonary cavity. It has been used more extensively in the study of bronchiectasis and the acute, subacute and chronic phases of lung abscesses. A review of the literature, however, failed to reveal any account of the routine bronchographic study of apparently healed abscesses. Overholt,⁸ to be sure, used bronchograms to determine the immediate results of operations upon lung abscesses. Farinas⁶ followed with bronchograms the course of lung abscesses through their acute, subacute and chronic phases.

Amberson¹ and his associates have not reported their extensive experience with bronchography in the follow-up of apparently healed lung abscesses during the past 7 or 8 years. They have quite regularly found residual cavities or bronchiectasis. It has been their experience that these cases are more likely to have a recurrence, much more likely to bleed in later years, and are more subject to slow convalescence from ordinary respiratory infections. In cases treated by various measures, shown to be healed (including bronchograms), and allowed sufficient convalescence, they seldom observed recurrence. Amberson recommends a 6 months' period of convalescence in cases of acute lung abscesses.

In the following group of case histories are reported the results of bronchographic study of 6 patients whose abscesses were regarded as healed, as judged by the usual criteria. The contrast medium used in all cases was lipiodol. Both the supraglottic drop method and the intra-tracheal catheter method were used. All injections were made under fluoroscopic control.

* Read at regular meeting of Grasslands Hospital Staff, September 28, 1938.

Case Abstracts. CASE 1.—D. H., a negro female, aged 36, was admitted to the hospital with a diagnosis of intestinal obstruction. Four days following a laparotomy, at which time the intestinal obstruction was reduced, she began to cough and expectorate blood-tinged sputum. A roentgenogram revealed pneumonitis in the right upper lobe. Within a week an abscess cavity appeared in this area (Fig. 1) and the patient was expectorating large amounts of foul sputum. She was treated by postural drainage and weekly bronchoscopies. Three months after admission the patient was asymptomatic and an ordinary roentgenogram revealed no abnormality other than light fibrosis at the site of the abscess (Fig. 2). A bronchogram 1 month later (Fig. 3) revealed a defect interpreted as a remnant of the abscess cavity, though the patient remained asymptomatic.

CASE 2.—T. P., a white female, aged 43, was referred to the hospital for cholecystectomy. An adenoma of the thyroid with toxic symptoms was discovered and a thyroidectomy was done. The cholecystectomy was deferred. The postoperative course was uneventful after the first few stormy days, and the patient was discharged. A few days later she was readmitted with fever, cough and purulent sputum. A roentgenogram revealed an abscess in the upper portion of the right lung. After 3 months on a regimen of postural drainage and weekly bronchoscopies, the patient was asymptomatic and the roentgenogram revealed only light fibrosis at the abscess site. Six months later the patient was still asymptomatic, but a bronchogram revealed bronchiectasis in the upper part of the right lung.

CASE 3.—M. G., a white female, aged 37, developed an abscess in the upper portion of the left lung, immediately following a tonsillectomy. The temperature rose to 104° F. daily and the sputum became copious and foul 1 week later. The results of postural drainage and bronchoscopies were unsatisfactory and the abscess was drained surgically 3 months after its onset. It was opened more widely 6 weeks later, in order to improve drainage. The patient was discharged as cured of her abscess, but with a residual broncho-pleuro-cutaneous fistula, 6 months after the onset of the abscess. The fistula closed 1 month later. A bronchogram revealed bronchiectasis and a cavity remnant at the site of the abscess, 21 months after discharge, though there had been no recurrence of symptoms.

CASE 4.—M. H., a white female, aged 30, gave a history of having had a lung abscess in the upper portion of the right lung 21 years previously. The abscess had been drained surgically with an uneventful recovery. Subsequently, the patient had frequent colds, during which she would expectorate purulent sputum. A small hemoptysis occurred soon after she came under our observation. Examinations of the sputum for tubercle bacilli were negative and roentgenograms revealed no abnormality except light fibrosis and postoperative deformities of the ribs in the right hemithorax (Fig. 4). A bronchogram (Fig. 5) revealed bronchiectasis and a defect interpreted as an abscess remnant in the upper portion of the right lung. At this time the patient was expectorating 60 cc. of foul pus daily.

CASE 5.—A.M., a white male, aged 33, was admitted to the hospital complaining of cough and the expectoration of 3 ounces of foul pus daily. His pulmonary symptoms had begun with an episode of more acute illness 18 months previously, but he had had no treatment. On admission, slight cyanosis was present and the fingers were clubbed. He was afebrile. A roentgenogram (Fig. 6) revealed pneumonitis surrounding a rarefaction in the upper part of the right lung. The patient remained on a sanatorium regimen of modified bed rest with postural drainage and weekly bronchoscopies for 5½ months. The sputum was repeatedly negative for tubercle bacilli and decreased to ½ ounce. Upon discharge the pneumonitis had cleared, but the rarefaction persisted (Fig. 7). A bronchogram 2½ years

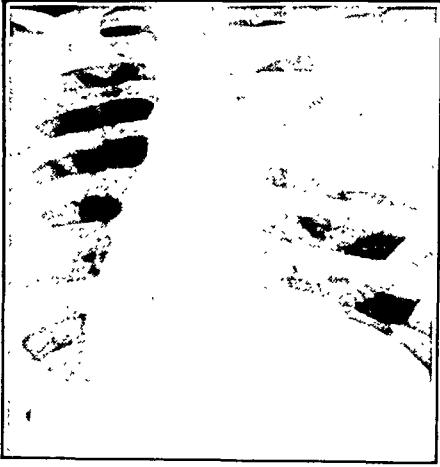


FIG. 1.—D.H.; acute lung abscess, upper part right lung.

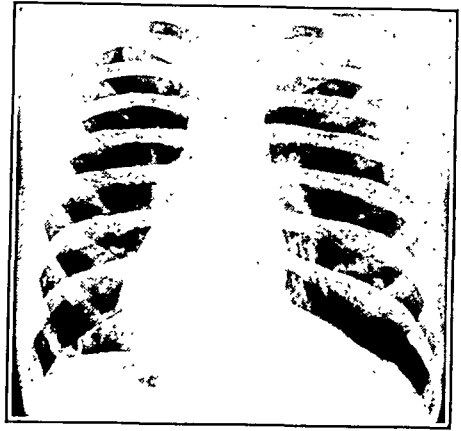


FIG. 2.—D.H.; 3 months later: lung abscess apparently healed.

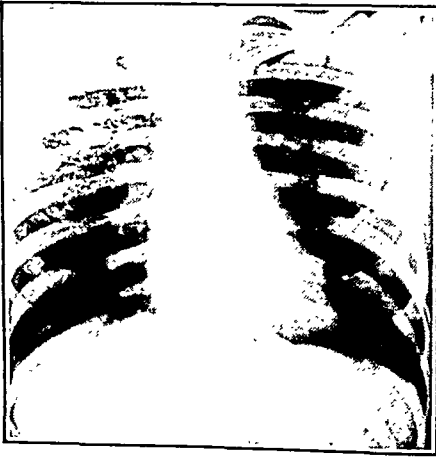


FIG. 3.—D.H.; 1 month later: bronchogram.

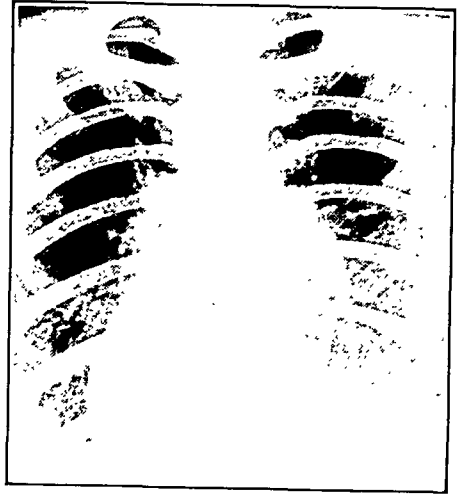


FIG. 4.—M.H.; 21 years after surgical drainage of lung abscess, mid-portion right lung.



FIG. 5.—M.H.; bronchogram.



FIG. 6.—A.M.; recurrent pneumonitis upper part right lung.

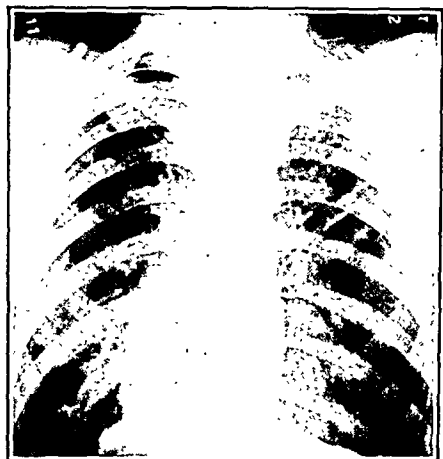


FIG. 7.—A.M.; after pneumonitis resolved, 5 months later.



FIG. 8.—A.M.; bronchogram, 2½ years later.

later (Fig. 8) revealed a large cavity remnant, as well as bronchiectasis, though the patient had remained asymptomatic.

CASE 6.—C. H., a white female, aged 44, was admitted to the hospital with the following history: 8 months previously she had a tonsillectomy under ether anesthesia. Two weeks later she developed a right upper lobe abscess with fever, cough and large amounts of foul sputum. Five weeks later the cough and expectoration ceased. Two months later the symptoms recurred, and continued until admission to Grasslands. Three weeks before admission, a 2-ounce hemoptysis occurred. Acid-fast bacilli were found in the sputum on 5 occasions before admission. Postural drainage and bronchoscopy were used for a few weeks after admission, but the abscess progressed and surgical drainage was done, with excellent clinical results. Acid-fast bacilli were found in the pus obtained from the abscess at operation, but these failed to produce tuberculosis in guinea-pigs. Ten months after admission the patient was discharged. Though she was asymptomatic, and the ordinary roentgenograms revealed only light fibrosis and post-operative rib deformities over the abscess site, a bronchogram revealed bronchiectatic sacs in the involved area. During a subsequent period of 2½ years, the patient has remained asymptomatic.

Discussion. The bronchopulmonary defects that can be demonstrated after healing of an abscess apparently has occurred, are of two kinds: cavitory and bronchiectatic. The cavitory defect probably represents an arrested stage of the fibrotic contraction of the abscess cavity. As such, it should be regarded as something less than the theoretically attainable end-result of healing. The cavitory remnant is not as commonly present as is the bronchiectasis. Pinner's concept⁹ of the unity of bronchopulmonary suppuration explains the frequent incidence of bronchiectatic remnants. He demonstrated that all phases of bronchopulmonary suppuration (pneumonitis, purulent bronchitis, bronchiectasis, abscess and gangrene) are characteristically present in some degree in most bronchopulmonary suppurative lesions. From the viewpoint of the pathologist, therefore, it is incorrect to designate one lesion as a lung abscess, another as bronchiectasis, and another as gangrene of the lung. It is the particular type of lesion which happens to predominate which determines the clinical diagnosis. Farinas⁶ showed that bronchiectasis commonly involves the bronchus draining an abscess and that bronchiectasis often develops in other parts of the lungs in cases of persistent abscesses.

The permanence of bronchiectasis is generally recognized. It may progress, or remain stationary, but regression of the bronchial defects is not to be expected. Rist's experience with the treatment of bronchiectasis by pneumothorax¹⁰ emphasized the characteristic persistence of bronchiectatic defects after symptoms referable to them have ceased. It is well known that these symptoms wax and wane as the infectious processes in and around the bronchi recur and subside. Churchill³ has emphasized the fact that bronchiectasis is a persistent and often progressive disease and that extirpation of the diseased portion of the lung offers the only real cure.

Reports of the cure of bronchiectasis are probably based upon the recession of symptoms rather than disappearance of the bronchiectasis. It seems logical, therefore, to look upon bronchiectatic residues after lung abscesses as being potentially dangerous and Amberson's experience has proven this.

Conclusions. 1. Bronchographic study after the disappearance of the symptoms and the roentgenographic shadows of acute suppurative bronchopulmonary disease often reveals residual pathologic defects in the lung and bronchi that are otherwise unrecognizable.

2. Bronchographic study should be used routinely to determine the residual state of the bronchi and lung after the symptoms and the roentgenographic shadows of the acute suppurative process have disappeared.

3. The clinical concept of healing of acute suppurative bronchopulmonary processes should be broadened to include the residual pathologic changes in the lungs and bronchi.

The author is indebted to the staff of the Medical and Surgical Services of Grasslands Hospital for the opportunity to study the presented cases.

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A CLINICAL STUDY OF ALUM-PRECIPITATED INSULIN.

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THE introduction of protamine-insulin marks an advance in the therapy of diabetes. Because of its slow rate of absorption, a single subcutaneous injection of protamine-insulin serves as a depot sufficient to supply the patient's needs for 24 hours or longer. However, there are certain features which occasionally detract from the value of this preparation. Its hypoglycemic activity does not begin until

about 6 hours after injection. In order to tide the patient over this initial period an additional injection of ordinary insulin is sometimes required. Furthermore, the duration of the hypoglycemic action of protamine-insulin is not always uniform so that insulin shock may occur as late as 24 hours after injection. Finally, some authors² have expressed the opinion that the parenteral administration over a number of years of small amounts of a foreign protein, such as protamine, may induce undesired reactions. Hence, it seemed of interest to investigate the therapeutic efficiency of other compounds of insulin precipitated with non-protein substances. For this purpose the alum-precipitated insulin, described in our earlier report,¹ was chosen.

Alum-precipitated insulin is prepared by adding 10 cc. of a 50% solution of $\text{NaAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ to 100 cc. of Insulin U 40. After remaining in the refrigerator for 24 hours the copious precipitate which forms is centrifuged off from the supernatant fluid. To the latter, another portion of 10 cc. of 50% soda-alum solution is added. After 24 hours of refrigeration a second precipitate is obtained by centrifuging. The combined precipitates are suspended in 50 cc. of saline of pH 6, preserved with 0.2% phenol and distributed into ampules for administration to patients. In preliminary experiments, it was found that by dissolving the combined precipitates in solutions of pH 1 to 2 and assaying the resultant clear solution on rabbits, a quantitative recovery of the original insulin unitage was obtained. Thus, one unit of alum-precipitated insulin refers to one unit of ordinary insulin precipitated by alum.

For the present investigation we selected 12 diabetic patients, most of whom required large amounts of insulin (up to 160 units) daily in 3 or 4 divided doses. Two of these patients were juvenile diabetics. All of them had been watched over a period of years in the dispensary of the Israel Zion Hospital where adjustments of their caloric and insulin requirements had been made from time to time.

Case Abstracts. CASE 1.—N. P., white female, aged 43, diabetic for 12 years, has been taking insulin since 1924. Average amount 150 units daily (8 A.M.—40 units, noon—30 units, 6 P.M.—40 units, 9 P.M.—40 units). In spite of this treatment has had from 2 to 9% of glucose in the urine, with a total daily output of 2 to 4 liters. Has frequently manifested shock symptoms, especially diplopia, when blood glucose fell below 170 mg. per 100 cc.; had been hospitalized 4 times in the past 3 years, twice in coma and twice in insulin shock. Weight 162 lbs. (74 kg.).

The first administration of the alum-precipitated insulin was given on November 6, 1936, when 160 units were injected at 10 A.M. in 1 dose. Meals were served to the patient according to her usual routine: breakfast, 100 calories at 9 A.M.; lunch, 900 calories at 2 P.M.; and dinner, 600 calories at 8 P.M. No untoward effects were observed. Neither local nor systemic reactions occurred. Hourly determinations of the blood glucose were made and the results were given in the chart. The patient was continued on this treatment for 2 months, during which time she showed a maximum of 1% and a minimum of a trace of glucose in the urine. The fasting blood glucose

ranged from 170 to 190 mg. in 100 cc. After this period she began complaining of slight dizziness, sweating and hunger at about 2 P.M. (5 hours after the injection of the alum-precipitated insulin).

The blood glucose at this time was 160 mg. per 100 cc. The daily dose of insulin was therefore reduced to 130 units in a single early morning injection. For a further period of 3 months the patient was maintained on the same amount of insulin. She felt quite well. Blood fasting sugar was 180 to 190 mg. per 100 cc. At the end of this period, because of reappearance of hypoglycemic symptoms, the insulin dosage was still reduced down to 100 units. In December, 1937, she developed an upper respiratory infection in the course of which the glucose tolerance was lowered and she had from 2 to 4% urinary glucose. The daily alum-precipitated insulin dosage was therefore raised to 130 units for the duration of the infection (9 days). This amount was reduced again to 100 units after the patient's condition improved.

At present, after about 2 years, she is still being comfortably maintained on 100 units of the alum-precipitated insulin. Present weight (September, 1938) 168 lbs. (77 kg.).

CASE 2.—L. B., a white female, aged 58, diabetic for 25 years, has been taking 50 to 75 units of old insulin daily since 1924 in 2 or 3 divided doses. Her urine has never been entirely sugar-free, excreting daily (between 1932 and 1936) from traces to 75 gm. of glucose. The treatment with alum-precipitated insulin was started November 11, 1936. Fifty units of alum-precipitated insulin were injected just before breakfast. Her regular morning, noon and evening meals were given at the usual time. No local or systemic reactions were noted. The blood glucose curve, after the injection, is given in the chart.

This amount of insulin was continued for a period slightly over 2 months. On January 14, 1937, she began complaining of tingling and numbness in the fingers and slight sweating and hunger. A blood specimen taken during one of these episodes showed 140 mg. %. The alum-precipitated insulin was therefore reduced to 35 units, on which dosage she is being maintained with a fasting blood sugar ranging between 130 to 180 mg. % and urinary glucose between 0 and 0.5 %. She is comfortable and has gained weight.

CASE 3.—Mrs. A. H., Jewish female, aged 48, diabetic for 10 years, obese and difficult to control; sensitive to all known varieties of insulin, manifesting a severe generalized urticaria after injections. She was slowly desensitized by injections of very minute doses of old insulin, beginning with 0.001 unit and slowly increasing the dose until she tolerated 60 units of old insulin daily. During the first 10 months in 1936, she was given 40 to 50 units of old insulin in 3 doses. During that period, her average fasting blood glucose was 258.6 mg. per 100 cc. and the daily urinary glucose output was 18 to 75 gm. On November 11, she was injected with 50 units of alum-precipitated insulin before breakfast. Her routine breakfast, dinner and supper were given and hourly blood glucose determinations were made. These appear in the chart.

After 3 months of treatment with alum-precipitated insulin, she began showing mild hypoglycemic symptoms (sweating, hunger, etc.). Therefore, her alum-precipitated insulin was reduced to 40 units daily. At no time did she show local or systemic ill effects. The patient is still being well maintained on this amount of insulin. Her last fasting blood glucose in September, 1938, showed 210 mg. % with a urine glucose of 0.5%.

CASE 4.—Mrs. C. F., white female, aged 63, a known diabetic since 1932, has been taking 20 to 45 units of old insulin daily in 2 doses; has had from traces to 3.3% of urinary glucose, with average fasting blood sugar (from 1932 to 1936) of 223 mg. per 100 cc. In 1936 (Sept. 12) she was injected with

30 units of alum-precipitated insulin, using the same routine as in the previous case.

Blood glucose fluctuation was determined as shown in the chart. On Sept. 25, 1936, she gradually developed hypoglycemic symptoms, drowsiness, hunger and sweating at about 4 P.M. At this time, she was aglycosuric with a blood sugar of 100 to 120 mg. %. Insulin dose was reduced to 24 units, on which amount she is still being maintained. Her present weight is 129 lbs. (as against 126 lbs. in 1936). She feels well.

CASE 5.—R. G., white female, aged 52, a known diabetic since 1927, has been using 45 to 55 units of old insulin in 3 doses daily, excreting 40 gm. of glucose daily. Fasting blood sugar, in the period of 1930 to 1936, ranged from 159 mg. to 233 mg. per 100 cc. On May 20, 1937, she was injected with 45 units of alum-precipitated insulin before breakfast. The blood glucose variations are shown in the chart. Has continued on this regimen since that time. She is comfortable and has gained 3 lbs. Last fasting blood glucose, Sept. 10, 1938, 130 mg. per 100 cc.

TABLE 1.—BLOOD GLUCOSE FINDINGS AFTER INJECTIONS OF ALUM-PRECIPIATED INSULIN.

Pt.	Case No.	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	8 hrs.	9 hrs.	10 hrs.	11 hrs.	12 hrs.	23 hrs.	24 hrs.
N. P.	1	262	278	286	288	270	211	190	142	148	138	140	142	242	258
L. B.	2	224	230	216	210	194	178	142	128	118	94	82	80	230	242
A. H.	3	264	278	242	222	190	184	172	152	132	124	118	138	228	250
G. F.	4	234	210	186	174	152	140	122	111	96	88	104	96	220	236
R. G.	5	182	170	158	166	148	132	118	98	90	96	94	108	194	188
D. G.	6	188	196	210	178	152	134	110	104	108	89	108	110	166	172
L. G.	7	234	231	210	172	134	120	108	104	102	101	96	107	188	194
R. C.	8	262	241	228	234	218	184	162	128	108	118	124	142	284	290
S. C.	9	310	298	248	228	196	178	166	170	164	154	196	190	286	278
J. R.	10	181	170	168	140	138	136	121	119	121	118	126	138	178	188
S. R.	11	168	144	156	139	138	121	101	99	108	118	138	146	160	166
A. A.	12	158	164	139	121	118	111	101	89	111	118	120	121	144	151

CASE 6.—Mrs. G., Jewish female, aged 62, known diabetic for 15 years, fairly well controlled during that period with 45 to 60 units of old insulin daily in 3 doses. Average fasting blood glucose 175 mg. per 100 cc., urine sugar ranging from traces to 1%. Sixty units of alum-precipitated insulin injected on Dec. 16, 1936. No untoward effects observed. Blood glucose curve is given in the chart. At present, 15 months later, she is still well maintained on single morning doses of 50 units of alum-precipitated insulin. She is comfortable and has gained 5 pounds in the last year.

CASE 7.—L. G., Jewish male, aged 22, a juvenile diabetic of 10 years' duration, weight 110 lbs., height 65 inches. Has been taking 120 units of old insulin daily in 4 doses of 30 units each at 9 A.M., noon, 4 P.M., and 8 P.M. Frequent episodes of coma and hypoglycemic tetany have occurred, necessitating hospitalization on several occasions. Average glycosuria 1 to 8%, with total daily urine output of 2 to 3 liters. Fasting blood glucose ranged from 180 to 330 mg. per 100 cc. On March 10, 1936, 120 units of alum-precipitated insulin were injected. The blood glucose variations are given in the appended chart.

Up to Sept. 17, 1937, the patient was well controlled. At 6 P.M. of that day, an insidious onset of hypoglycemia manifesting itself by drowsiness deepening into stupor. After taking 2 glasses of orange juice, containing 40 gm. of glucose, the patient quickly rallied. No further ill-effects were

noticed and the daily dosage of alum-precipitated insulin was thereafter cut to 100 units. Since then, has been kept on the same high caloric, high carbohydrate diet with 100 units of alum-precipitated insulin daily administered in one early morning injection. Is feeling well and has been doing daily work, without interruption.

CASE 8.—R. C., Jewish white female, aged 12, an extremely severe juvenile diabetic of 7 years' duration, has been taking a total of 200 units of old insulin daily in 4 or 5 doses. Has manifested marked xanthochromia of several years' duration. In 1935 and 1936 was hospitalized 4 times because of diabetic coma. Diet consists of 1800 calories daily. Twenty-four-hour urine had from 2 to 5% glucose and, at times, as much as 9%. Average fasting blood glucose 250 mg. per 100 cc. On Dec. 14, 1936, 160 units of alum-precipitated insulin were injected. Blood glucose variations of that day appear in the chart.

After 10 months the child is still maintained well on the same diet and the same amount of alum-precipitated insulin, with an average 24-hour urine sugar of 0.5 to 1% and an average fasting blood sugar of 180 mg. per 100 cc. On two occasions infections at the site of the injections were observed. This was traced to faulty technique in the administration of the insulin by the patient's mother. The child has gained weight, felt well and was able to attend school uninterruptedly for the past 2 years, which was impossible under previous treatment with old insulin.

CASE 9.—S. C., white female, aged 55, a known diabetic of 5 years' duration. Condition was complicated by peripheral vascular and coronary diseases. Treatment consisted of 100 units of old insulin daily, in 3 doses. Has been hospitalized twice in the past 2 years for attacks of coronary thrombosis. Diet consisted of 1500 calories. Average 24-hour urine sugar in the past 3 years showed from traces to 1%. Average blood sugar 180 mg. per 100 cc. On Dec. 10, 1936, 120 units of alum-precipitated insulin were given in a single morning injection. Subsequent blood glucose of that day appears in the chart. No untoward effects were observed. Since then, has been maintained well on the same diet and the same amount of alum-precipitated insulin. Several repeated urine glucose tests in the past 16 months show from traces to 0.5%, with a fasting blood glucose of 160 mg.

CASE 10.—J. R., white male, aged 58, a known diabetic of 4 years' duration with fasting urine glucose fluctuating from 1.5 to 3%. Blood glucose May, 1937, was 189 mg. per 100 cc. Has been using 15 to 30 units of old insulin. On June 23, 1937, 20 units of alum-precipitated insulin were injected in 1 dose before breakfast. Blood glucose fluctuations of that day are given in the chart. Patient has been well maintained on a diet of 1500 calories, including 185 to 190 gm. of available glucose and 20 units of alum-precipitated insulin. Is comfortable and does his daily work without difficulty.

CASE 11.—S. R., Jewish male, aged 52, a known diabetic for 15 years, excretes an average of from 10 to 15 gm. of glucose daily, with a fasting blood glucose of 185 mg. Average ordinary insulin requirement had been 25 units daily in 2 doses. On March 17, 1937, 25 units of alum-precipitated insulin were injected, following the same technique as outlined above. Blood glucose curve of that day is given in the chart. Patient was maintained on his previous diet with 25 units of alum-precipitated insulin daily in a single injection. Is doing well, is able to do his usual work and has kept his weight stationary during the past 18 months (151 lbs.).

CASE 12.—A. A., Jewish female, aged 49, a known diabetic of 4 years' duration, has been excreting an average of 10 to 20 gm. of glucose daily in the urine, with an average fasting blood glucose of 160 mg. per 100 cc. Average old insulin requirement was 20 units daily in 2 divided doses. On March 21, 1937, 20 units of alum-precipitated insulin were injected. The resulting blood curve is given in the chart. Since that time, has been receiv-

ing the same amount of alum-precipitated insulin daily in one single injection. Condition remained good. Urine rarely showed glucose, and fasting blood sugars averaged 130 mg. per 100 cc.

Discussion. While the number of cases here reported is limited, yet the long periods of treatment during which several thousand injections were given and the uniform results obtained yield sufficient information to demonstrate the value of alum-precipitated insulin. The following facts stand out:

1. Alum-precipitated insulin is a safe preparation. It was administered in each case in a single morning injection equivalent to the total daily unitage of the old insulin which had previously been given in several injections. As much as 160 units of alum-precipitated insulin were used in a single dose (Case 1) without untoward effects, local or general.

2. The lowering of the blood glucose with corresponding drop of the urine glucose begins within 2 hours after injection of the alum-precipitated insulin. Thus, in not one of our cases was the use of a supplementary dose of ordinary insulin necessary. The hypoglycemic action reaches its maximum effect in 8 hours, after which it gradually wears off.

3. The effect of alum-precipitated insulin is more evenly distributed through the 24 hours. There were not noted marked fluctuations of the blood sugar or any delayed action beyond the 24-hour period. In this respect, it differs from protamine-zinc insulin, the injection of which not infrequently causes a delayed hypoglycemic action with symptoms of shock.

4. On only one occasion manifestations of hypoglycemic tetany were encountered, in a patient (Case 7) who had several hypoglycemic shocks during the 10 years of old insulin therapy. The shock was of short duration and the patient rallied quickly. Subsequently, the patient was able to tolerate the same dose of alum-precipitated insulin without ill effect.

5. In the course of treatment we were obliged to reduce the amount of alum-precipitated insulin which originally had been just sufficient to keep the diabetic status under control.

6. The physical and mental condition of the patients was good throughout the whole period of treatment. Some gained weight while others, who did not show any appreciable gain in weight, felt a general euphoria and were comfortable enough to perform their daily work.

Summary. 1. Alum-precipitated insulin like protamine-zinc insulin can be administered in one single dose covering the daily requirement.

2. The action of alum-precipitated insulin begins within 2 hours which obviates the necessity of administering a supplementary injection of old insulin.

3. The effect of alum-precipitated insulin wears off within 24 hours so that the fear of a delayed reaction is eliminated.

4. In the course of treatment with alum-precipitated insulin, the tolerance of the patients seems to improve and the amount of insulin may be reduced.

5. Alum-precipitated insulin contains no foreign protein which might have an undesirable effect in the course of prolonged administration.

6. Alum-precipitated insulin is stable, non-toxic even after prolonged administration and does not cause infiltrates at the site of injection.

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CIRCULATORY EFFECTS OF VOLATILE AMPHETAMINE (BENZEDRINE INHALER).

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IN recent years a volatile compound, beta-phenyl-iso-propylamine (amphetamine), in the form of "benzedrine inhaler", has come into widespread use for the relief of congestion of the nasal mucous membranes. In view of the fact that this drug is closely related chemically and in some of its pharmacologic properties to the sympathomimetic drugs, ephedrine and epinephrine, it was considered advisable to inquire into its effects on the circulation, particularly in individuals with heart disease. The dangers attendant upon the administration of epinephrine and ephedrine in the presence of angina pectoris are now coming to be fully recognized and it appeared possible that under the same circumstances the "benzedrine inhaler" might produce undesirable reactions.

The scope of this study was limited to an investigation of the benzedrine inhaler. The circulatory effects of "benzedrine sulphate" have already been investigated elsewhere. Myerson *et al.*¹ observed the effects of benzedrine sulphate administered subcutaneously to 18 patients in doses of 9 to 50 mg. A gradual rise in the systolic blood pressure varying from 10 to 64 mm. Hg was noted in all but 1 case. The maximum rise was reached in 11 to 85 minutes and the pressure had returned to the original level in 1½ to 7½ hours. There was no commensurate rise in the diastolic

pressure. The pulse rate decreased coincident with the rise in systolic pressure in 12 cases, remained unchanged in 4 cases and increased in 2 cases. The decrease in pulse rate varied from 4 to 25 beats per minute.

There is no qualitative difference between the pharmacologic effects of benzedrine inhaler and benzedrine sulphate once absorbed into the circulation, but the amount of the drug actually absorbed from the inhaler is very small. Each tube of the inhaler contains 325 mg. of benzedrine. It has been estimated that at each average inhalation from a fresh tube 0.05 mg. is taken out of the tube. Some of this is lost in exhalation and probably only a relatively small fraction enters the circulation.² According to the directions on the tube, not more than 2 inhalations from each nostril should be taken within the course of 1 hour, making a maximum recommended dose of 0.2 mg. per hour. The effects of fantastically large amounts of the benzedrine inhaler in a normal individual were investigated by Waud,³ who in repeated experiments with a tube of benzedrine inhaler in each nostril inhaled entirely through the tubes for periods of 4 to 6 hours. He estimated that the dose taken was 1000 times the recommended therapeutic dose. He noted a rise in the pulse rate and in both systolic and diastolic blood pressures. He also developed extrasystoles which persisted for 4 or 5 days after an experiment and on 2 occasions had paroxysmal tachycardia following cessation of the inhalations.

Procedure. A total of 67 individuals was studied. Ten of these were controls without heart disease, 10 cases of rheumatic heart disease, 1 syphilitic, 10 hypertensive, and 36 cases of arteriosclerotic heart disease, 8 of them with congestive failure without angina and 28 with angina pectoris.

In each case, a control record was made of the pulse, blood pressure and electrocardiogram. Then the patient took 5 deep inhalations of benzedrine inhaler in each nostril in the course of 2 minutes. Fresh inhalers were used in each case. Electrocardiograms were recorded during and immediately after the inhalations, 5 minutes, and one-half hour later. Blood pressure readings were noted before and 5 minutes after the inhalations.

RESULTS. Controls. One intern and 9 patients convalescing from various non-circulatory diseases were used as controls. Six of them were males and 4 females and they were from 23 to 40 years of age. Changes in the pulse rate and blood pressure levels were so slight and so variable as to be regarded as entirely without significance. There was no change in the electrocardiogram.

Rheumatic Heart Disease. There were 10 patients with rheumatic heart disease; 2 of these had active rheumatic fever and 2 others had auricular fibrillation. Three were females and 7 males, the ages varying from 13 to 58 years. Following the inhalation of benzedrine there was no significant alteration in pulse rate or blood pressure. Electrocardiograms showed slight changes in 2 instances. In 1 case the *T* wave in Lead III which was inverted in the control

record changed to an upright deflection in subsequent records. In another case, there was a slight but definite shift in the axis to the left at the end of one-half hour. These changes were not regarded as definitely significant.

Syphilitic Heart Disease. In 1 case of a man of 46 with syphilitic aortic regurgitation and congestive failure, no significant changes in pulse, blood pressure or electrocardiogram were observed following the use of benzedrine inhaler.

Hypertensive Heart Disease. This group included 10 cases, 6 female and 4 male aged from 15 to 70 years. In each case, the systolic blood pressure was above 210 mg. Hg or the diastolic pressure was above 105 mg. Hg. The youngest patient had chronic glomerular nephritis. Four of the cases were in congestive failure at the time the tests were made. In this group, likewise, benzedrine inhaler had no effect on pulse, blood pressure or electrocardiogram.

Arteriosclerotic Heart Disease. This group consisted of 36 cases, 28 of whom were suffering from typical angina pectoris. Of the 8 cases without angina, 2 had had a previous coronary thrombosis and all had had symptoms or signs of cardiac failure. None of these 8 showed significant changes in pulse, blood pressure or electrocardiogram following the inhalation.

Angina Pectoris. Fifteen of the cases with angina pectoris were female and 13 were male, the ages varying from 37 to 76 years. Eight of them had had a previous history of coronary thrombosis. No significant alterations in pulse rate, blood pressure or electrocardiogram were noted in this group. In 1 patient, however, the inhalation of benzedrine was followed by an attack of angina pectoris. The following is a summary of the observations in this case.

CASE 1.—A 48-year-old housewife had had a typical attack of coronary thrombosis 14 months before, following which she had attacks of pain in the left chest radiating down the left arm. These attacks were associated with a choking sensation. They were precipitated by exertion or eating and lasted only a few minutes. During the first test she complained of slight precordial distress after 5 or 6 inhalations of the benzedrine (over a period of less than 2 minutes). On the next day, the same procedure was carried out using a tube which to all outward appearance was the same as the one used the day before, but which contained only the menthol and lavender with which the benzedrine is regularly compounded. No reaction was noted with this control. About 10 minutes later she was given a tube containing the regular formula to inhale and after 6 or 7 inhalations experienced an attack of moderately severe precordial pain which was relieved after the administration of $\frac{1}{100}$ gr. of nitroglycerine. No changes in the electrocardiogram were observed in association with these attacks.

About 3 weeks later another test was carried out. On this occasion, she developed a typical attack of angina following 3 inhalations of the benzedrine. The pain was relieved by nitroglycerine, gr. $\frac{1}{60}$. The electrocardiogram showed no change. The significant feature of this test was that angina appeared to be precipitated by an amount of benzedrine in the range of the therapeutic dose recommended by the manufacturer. About 10 minutes later the patient was given 6 inhalations of a "blank" tube containing only menthol and lavender without provoking any symptoms.

Discussion. It seems justifiable to interpret the painful attacks which in this case appeared to be related to the inhalation of benzedrine as angina pectoris. In 3 other cases precordial symptoms attended the initial use of the inhaler, but subsequent control tests using both the regular and "blank" tubes failed to substantiate any relationship between the drug and the symptoms. It is of some interest that the patient who was most incapacitated by his angina had no symptoms from inhalation of benzedrine, nor did the patient with the most abnormal electrocardiogram.

Summary and Conclusion. The effects on the circulation of volatile amphetamine (benzedrine inhaler), in larger than therapeutic doses, were studied in 10 individuals with normal hearts and 57 patients with various forms of heart disease.

No significant effect on the pulse or blood pressure and only occasional, slight and probably insignificant effects on the electrocardiogram were observed.

In 1 of 28 cases of angina pectoris, attacks of angina appeared to be precipitated by the drug.

The above observations lead to the conclusion that heart disease *per se* is not a contraindication to the use of benzedrine inhaler in therapeutic doses. Nor does there appear to be any pressor effect to contraindicate its use in hypertension. On the other hand, in patients who have had angina pectoris it should be used with caution, if at all, since in occasional cases it may precipitate an attack.

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BOOK REVIEWS AND NOTICES

PRACTICAL MICROBIOLOGY AND PUBLIC HEALTH. For Students of Medicine, Public Health and General Bacteriology. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas; Visiting Bacteriologist of John Sealy Hospital, Galveston; etc. Pp. 492; 125 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

THIS book is intended to accompany courses in "Preventive Medicine" or "Public Health," being given to medical students. The author presents the volume only as a handbook "designed to aid the student in organization, interpretation, and systematic record of data from laboratory and field." It is in no sense a textbook, nor does it do more than present the barest essentials, in synoptic form, of such a variety of subjects as general and clinical bacteriology and mycology; vehicles of infection; immunology; the methods used by the public health laboratory in examining milk, water, and foods, and in making various diagnostic tests; public health field surveys; garbage removal; ventilation; housing; restaurants; vital statistics; epidemiology; protozoology; helminthology; etc. It is expected of the student that he be previously "Familiarized by lecture and standard tests with the findings of authorities. . . ." The book is attractively printed and bound, and instructively illustrated. A number of laboratory exercises are detailed or suggested, and an index is appended. K. M.

SYNOPSIS OF CLINICAL LABORATORY METHODS. By W. E. BRAY, B.A., M.D., Professor of Clinical Pathology, University of Virginia; Director of Clinical Laboratory, University of Virginia Hospital. Pp. 408; 51 illustrations and 17 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

THE text covers the entire range of practical procedures in Clinical Pathology, including most of the more recently developed methods. Alternate techniques for the same purpose are well selected and not too numerous. The text is brief, concise. Illustrations and tables are good. The book is commendable for its information in the selection and interpretation of methods, thus emphasizing the practical application of Clinical Pathology in diagnosis. W. B.

DIE ENDOKRINEN DRÜSEN DES GEHIRNS. Epyphyse und Hypophyse. Ein Blick in ein interessantes Gebiet. By DR. MED. PAUL NIEHANS, Chirug. F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 280. Bern: Medizinischer Verlag Hans Huber, 1938. Price, Fr. 10.50.

THE author has attempted an exceedingly difficult task, that results in an essentially uncritical compilation of conclusions from the abundant literature concerning the pituitary and pineal glands. The discussion of the etiologies of clinical syndromes is replete with statements based on very poor evidence. No bibliography is given. F. D.

DISEASES OF THE EAR, NOSE AND THROAT. By FRANCIS L. LEDERER, B.Sc., M.D., F.A.C.S., Professor and Head of the Department of Laryngology, Rhinology and Otolaryngology, University of Illinois College of Medicine; Chief of the Otolaryngological Service, Research and Educational Hospital. Pp. 835; 457 illustrations, and 16 color plates. Philadelphia: F. A. Davis Company, 1938. Price, \$10.00.

THE author of this textbook has courageously adopted numerous innovations which tend to enhance the value of a reference volume. Although profusely illustrated, there is no attempt at illustration of surgical procedures which, with slight variations, are portrayed with monotonous regularity in most otolaryngological textbooks. The author achieves throughout a clear presentation of etiology, pathology, symptomatology, diagnosis, prophylaxis and treatment. While the appropriate surgical measures are described where indicated, they are relegated to minor emphasis. The author's clear exposition of the anatomy and physiology of the ear, the nose and paranasal sinuses, the pharynx and the larynx is especially instructive and satisfying. The text is arranged in two columns to facilitate reading; the illustrations are excellent. A determined attempt has been made to present the fullest details in diagnosis, differential diagnosis and therapy. The subject matter includes such considerations as diseases of the tongue, and of the salivary glands and ducts. The technique and instrumentation of bronchoscopy and esophagoscopy are described; separate chapters are devoted to otolaryngological symptoms common to many diseases, facial neuralgias, allergy, disorders of speech, psychiatric aspects and legal medicine. While no bibliographic references are given, the index is complete and detailed. This volume is an outstanding addition to the textbooks in the field of otolaryngology.

H. S.

DENTAL SCIENCE AND DENTAL ART. Edited by SAMUEL M. GORDON, Ph.D., National Research Council Fellow (Biological Sciences), 1926-1928; Director, American Dental Association Bureau of Chemistry and Secretary of the Council on Dental Therapeutics, American Dental Association, 1928-1937. Nineteen Contributors. Pp. 731; 224 illustrations and 61 tables. Philadelphia: Lea & Febiger, 1938. Price, \$9.50.

THOSE who still believe that modern dentistry has not emerged from the mere mechanical stage should read this elaborate composium edited by Dr. Gordon. It is written in the form of separate essays on the physiologic, pathologic and therapeutic problems in dentistry which point definitely to a new era in dental science and dental art.

Dr. Gordon's selection of authors and especially his correlation of subject matter is commendable. Most essays mention possibilities of investigation, thus stimulating research in their respective fields.

Schour covers tooth development and the effect of avitaminosis and endocrine inadequacies on developing and adult teeth, their attachment apparatus, the form and function of the dental arches, the jaws and the cranium. In his discussion of dental fluorosis he fails to refer to the exhaustive essay of Chaneles on fluorine and experimental fluorosis, which anteceded his work by four years. Schour's attitude appears too definite in regard to the impossibility that calcium may be withdrawn from tooth structures. In 1938 Hevesy, Holst and Krogh showed that radio-activated phosphorus atoms are exchanged. The condensed results of various studies of Roentgen ray diffraction patterns throw an interesting light on the crystal structures of enamel and dentin. Gottlieb and Orban write on the biology of the investing structures of the teeth and outline some pathologic conditions of these tissues. Brodie presents the biologic aspect of orthodontia. Here we should like to have seen the subject of diet treated more extensively

and regret the omission of nutritional considerations. Babkin's essay on the physiology of the salivary gland seems both up to date and comprehensive. His list of references is creditable. The subject of salivary calculus is well presented by Karshan. Rosebury reviews the problem of dental caries extremely well; the biochemical aspects of dental caries are done by Karshan; the bacteriologic and immunologic features by Jay, who states at the end of his chapter: "It is still problematical whether the immunologic approach will yield practical results, and as stated at the beginning, the whole problem of immunity in dental caries is atypical but the pursuance of these studies may ultimately lead to findings of considerable significance." Gordon reviews the essential factors in calcium metabolism, absorbability of calcium salts, inorganic *vs.* organic calcium phosphorus combinations, nutritional and pharmacodynamic actions of calcium compounds, and guided by an array of modern writers on the subject discusses the aspects of calcium metabolism of direct interest to the dentist. The bacteriologic aspect and possible predisposing factors of Vincent's infection are well covered by Rosebury, whereas Lyons' essay on the clinical manifestations, pathologic phenomena and therapeutic measures of Vincent's infection supplements Rosebury's chapter quite ably. The chapter on selected diseases of the mouth by Cornbleet could be better organized and more up-to-date. We have never seen malignant epulides and do not believe that mixed tumors are prone to become malignant. Dean's contribution on chronic dental fluorosis omits the results of animal experimentation. Lyons could have done better on the subject of the pulpless tooth and factors concerning its therapy. A discussion of contraindications to the treatment of pulpless teeth should not have been omitted. The properties of restorative materials are discussed by Peyton. Seevers writes a review on the principles of inhalation anesthesia; Tuoty on its clinical aspects in dentistry; Tainter and Moose on local anesthesia. These three chapters give an informative and complete survey of the field. Antiseptics and disinfectants are handled by Hull, who treats of their physical and chemical properties and dwells at some length on the phenol coefficient and other tests for disinfectants. The chapter on statistical methods in dentistry by Gafafer should be helpful in eliminating to some extent the contradictory conclusions frequently recorded in professional journals.

H. C.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID. By JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University and Chief of the Medical Services, Massachusetts General Hospital, and EDWARD P. RICHARDSON, M.D., John Homans Professor of Surgery, Harvard University, and Chief of the West Surgical Service (Massachusetts General Hospital). (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 367; 51 illustrations. New York: Oxford University Press, 1938. Price, \$5.00.

THIS is a revision, separately reprinted, of a monograph which originally appeared in the Oxford Monographs on Diagnosis and Treatment in 1929. The authors are well known for their contributions to the medical and surgical aspects, respectively, of thyroid disease. The volume represents a clear, but not too detailed, review of the more important clinical aspects of thyroid disease, with emphasis upon the practical problems. The value of the work is enhanced by judiciously selected case histories. Although it lacks somewhat the flavor and discursive style of the senior author's excellent book on the Thyroid and Its Diseases, it can be recommended for the practitioner or student who wishes to keep abreast of the soundest current thought in its field.

E. R.

CONSOLIDATED INDICES. Embracing Transactions of the American Roentgen Ray Society (1903-1908); American Quarterly of Roentgenology, Vols. I-V (1906-1913); American Journal of Roentgenology, Vols. I-IX (1913-1922); American Journal of Roentgenology and Radium Therapy, Vols. X-XXXVIII (1923-1937). Author and Subject: 1903-1937. Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, 1939. Pp. 451. Springfield, Ill.: Charles C Thomas, 1939. Price, \$12.50.

This book has been compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, who are to be congratulated on their service to medicine. The work has been prepared by a real authority and should be of great assistance to any one looking up the subjects in radiology, especially in the early periods before comprehensive indices were available. The entire work has been done in a most meticulous manner. E. P.

CLINICAL BACTERIOLOGY. By F. A. KNOTT, M.D., M.R.C.P., D.P.H., Director, Bacteriological Department, and Lecturer in Bacteriology, Guy's Hospital. Pp. 426; 60 illustrations, including 12 plates. Philadelphia: P. Blakiston's Sons & Co., Inc., 1939. Price, \$4.50.

THE author's attempt to present the clinical significance of bacteriologic phenomena has not, in the Reviewer's estimation, been successful. The book is too incomplete for use as a textbook; it will be of little use to clinical pathologists because of the lack of laboratory procedures; and it offers nothing to clinicians which they can not obtain from any good textbook of medical bacteriology. Its value is further reduced because of an absence of bibliography. Inconsistencies and errors appear through the book, too numerous to detail here. [The Reviewer gave some 8 or 10 examples by way of illustration, but they have been deleted to save space. EDITOR.]

The contents of the book possess nothing for which it can be recommended in this country. H. M.

STUDIES OF TRAUMA AND CARBOHYDRATE METABOLISM WITH SPECIAL REFERENCE TO THE EXISTENCE OF TRAUMATIC DIABETES. By VIGGO THOMSEN. Pp. 416; illustrated. Copenhagen: Ejnar Munksgaard, 1938. Price, d. Kr. 15.

THE opening account of the general history of trauma as related to diabetes affords a clear, well documented background of the medical and legal problems which have arisen when trauma has preceded the discovery of glycosuria. The author's work includes various studies of the blood and urine sugar in 144 injured normal persons and case reports of 100 injured diabetics. He also summarizes 81 case reports of so-called traumatic diabetes from the literature. There is a chapter on his investigations concerning the mechanism of post-traumatic disturbances in man. He regards overactivity of the sympathetic nervous system as the cause of the hyperglycemia. Some of the patients were tested for their tolerance to glucose with and without ergotamine in an effort to demonstrate this point; the author rightly regards these results as inconclusive. In a judicious summary, the conclusion is reached that except for the theoretic case of pancreatic injury, trauma cannot cause diabetes nor can it cause more than a temporary exacerbation of an existing diabetes.

There are some minor typographical errors, but the book combines a sound appraisal of the problem with good original clinical observations which combine to make one respect the author's opinion. Physicians, surgeons and those concerned with forensic medicine will find this a valuable reference work. F. L.

STUDIES ON THE SIZE OF THE RED BLOOD CELLS ESPECIALLY IN SOME ANAEMIAS. By ERIK MOGENSEN. Pp. 216; 43 illustrations. Copenhagen: Ejnar Munksgaard; London: Oxford University Press, 1938.

THE size of the red blood cells—both volume and diameter—has become of greatly increased clinical importance in the past decade, since it was recognized that it was a valuable measurement both in the diagnosis and control of treatment in various anemias. Following a description of the various techniques—especially the Price-Jones curves, the author has analyzed the studies by himself and others in health and disease. Thus he finds that the average mean diameter of normal human red cells is $7.15\ \mu$ (Stand. dev., $0.46\ \mu$) and that in untreated pernicious anemia the cell population can be split into two more characteristic size groups. The effects of lack of iron in pernicious anemia, cancer, and so on as well as in simple hypochromic anemia, are analyzed. Without settling anemia problems, this book is a sound objective contribution to an active phase of anemia study

E. K.

THE FUNCTIONS OF HUMAN VOLUNTARY MUSCLES. By NORMAN D. ROYLE, M.D., CH.M., F.R.A.C.S., Honorary Demonstrator of Anatomy, University of Sydney; Senior Orthopedic Surgeon, Lewisham Hospital, Sydney, etc. Pp. 42; 11 illustrations. Sydney: Angus & Robertson Ltd., 1938. Price, 3/6.

THE author collaborated with J. I. Hunter in his work on the sympathetic innervation of voluntary muscles in 1934. Professor Burkitt in his foreword recounts that the author's interest in muscles began in his student days, and this interest extended to his personally developing considerable control of individual muscles. With such a background it is not surprising that this little volume contains much of practical value and much that is omitted from the more academic expositions. Its simplicity and directness is apparently the result of complete familiarity with the field. A beginning medical student could read it with enjoyment and the practitioner or specialist in anatomy or orthopedics could read it with profit. O. B.

INSULIN. Its Chemistry and Physiology. By HANS F. JENSEN, PH.D., Associate, Laboratory for Endocrine Research, The Johns Hopkins University, Pp. 252. New York: The Commonwealth Fund, 1938. Price, \$2.00.

IT is fitting that a monograph upon the structure and properties of insulin should emanate from the laboratory of the late Professor Abel of Hopkins who in 1922 isolated this hormone. Dr. Jensen's monograph is timely and of great value. G. W.

SYNOPSIS OF PULMONARY TUBERCULOSIS. By JACOB SEGAL, M.D., Physician in Charge of Fordham Hospital Tuberculosis Clinic, New York; Associate Visiting Physician, Riverside Hospital, New York, and Bronx Hospital. Foreword by the late POL N. CORYLLOS, M.D., F.A.C.S., Professor of Clinical Surgery, Cornell Medical College; Director of Thoracic Surgery at Seaview and Metropolitan Hospitals, New York, etc. Pp. 150; 21 illustrations. New York: Oxford University Press, 1939. Price, \$2.75.

IN this small volume a difficult task has been accomplished creditably. The author has attempted to condense in very limited space the accepted facts on tuberculosis as respects its pathogenesis, clinical types, diagnosis,

complications, treatment and prevention. By excluding controversial subjects he has been able to present a reasonably well rounded picture to which little exception can be taken. Obviously this small monograph is not a reference book, but it is useful for beginners in tuberculosis, and particularly for those not intending to specialize in the disease, but anxious to be brought up to date in the field. The book is copiously illustrated with reproductions of Roentgen ray films. The style is simple, if at times colloquial; the meaning is always clear. A foreword by the late Dr. Pol N. Coryllos is prefixed to the text. E. L.

THE WISDOM OF THE BODY. By WALTER B. CANNON, M.D., Sc.D., LL.D., DR. (HON.), George Higginson Professor of Physiology, Harvard Medical School. Pp. 333; 40 illustrations. New York: W. W. Norton & Co., Inc., 1939. Price, \$3.50.

THE valuable account of the means utilized to maintain constant conditions in the body (homeostasis), which Dr. Cannon gave in 1932 has been reprinted with some modifications and additions. In general the form remains the same with its lucid expression of physiologic facts in terms mostly understandable by the layman. The additional material mainly deals with the effects of age on such adaptations and a comparison of the capacities of the dog and cat to adjust to difficult conditions. As in the original volume the evidence is mainly drawn from the brilliant series of researches of Dr. Cannon and his co-workers. H. B.

SURGICAL TREATMENT OF HAND AND FOREARM INFECTIONS. By A. C. J. BRICKEL, A.B., M.D., Departments of Anatomy and Surgery, Western Reserve University. Pp. 300; 166 illustrations and 35 plates (10 in color). St. Louis: The C. V. Mosby Company, 1939. Price, \$7.50.

HERE is an authoritative monograph: well written and beautifully illustrated. The basic work of Kanavel, on infections of the hand, has been greatly supplemented and advanced. The section on surgical treatment is excellent. G. W.

CLINICAL GASTRO-ENTEROLOGY. By HORACE WENDELL SOPER, M.D., F.A.C.P., Pp. 314; 212 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$6.00.

DR. SOPER's work is short, to the point, and very readable. It is, however, rather a condensation of personal impressions, chiefly on therapy, than a didactic presentation of the diseases of the digestive tract. Many sections, such as those on peptic ulcer, intestinal obstruction, hepatic and biliary disease are rather sketchy. The only liver disease described, for instance, is *tania echinococcus* infestation. The best feature of the book is the large number of excellent Roentgen ray photographs. The general practitioner will find many interesting therapeutic and dietary suggestions, especially on diseases of the colon. Specialists will insist on a more complete coverage of the field of gastro-enterology. J. D.

CONSULTATION ROOM. By FREDERIC LOOMIS, M.D., Diplomate of the American Board of Obstetrics and Gynecology. Pp. 281. New York: Alfred A. Knopf, 1939. Price, \$2.50.

ONE begins reading this book to find, if one is a physician, a rather commonplace account of the circumstances surrounding a youth who *knew* he wanted to be a physician and of the various difficulties to be overcome. To the laity, however, these opening chapters will doubtless have more interest and color. Established as an obstetrician-gynecologist, the author has

stories to tell—dramatic human problems naturally revolving about sex—that will arouse and captivate the interest of the layman and the human physician alike. The problems of pain and death, honor and spiritual distress, selected from the thousands of cases that the author has seen in the many years of his special practice on the Pacific Coast, are described in a simple, yet fresh and vigorous style. Little is said directly about the author's private life, though his personality emerges distinctly as the tale proceeds. In the latter half of the book, which has long since "sold" itself to the reader, much sound information on what every woman should know is skillfully and innocuously interlarded with the illustrative incidents that fill the text. Few woman readers, and few mere males, too, for that matter, will fail to be charmed and instructed by this unusual book. E. K.

THE PRINCIPLES AND PRACTICE OF OPHTHALMIC SURGERY. By EDMUND B. SPAETH, M.D., Associate Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia; Consultant in Ophthalmology to the Philadelphia Hospital for the Insane (Byberry), etc. Pp. 835; 413 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$10.00.

This book is unquestionably the best in the English language on ophthalmic surgery. It covers the entire field from plastic surgery of the lids to all forms of operations on the globe. The illustrations are excellent and the descriptions of the operative procedures are clear and concise. It cannot be too highly recommended. F. A.

PULMONARY TUBERCULOSIS IN ADULTS AND CHILDREN. By JAMES ALEXANDER MILLER, A.M., M.D., D.P.H., Sc.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; late chief of, now Honorary Consultant to, the Tuberculosis Service, Bellevue Hospital, New York, and ARVID WALLGREN, M.D., Head of the Children's Hospital, Gothenburg, Sweden. Pp. 196; 77 illustrations. New York: Thomas Nelson & Sons, 1939. Price, \$3.50.

THIS book consists of a modification of separate sections recently contributed by Dr. Miller and Dr. Wallgren to the Nelson Loose Leaf Medicine. It is interesting that two authors, widely separated geographically, have found their views so compatible in the related fields of tuberculosis in adults and in children as to warrant a joint publication. Both are well known to American readers, Miller for his writings in the general field of tuberculosis and particularly hematogenous tuberculosis, and Wallgren for his studies on primary tuberculosis. Miller's section of the present volume covers infection and the pathogenesis, clinical course, diagnosis and treatment of tuberculosis as it occurs in adults; while Wallgren's section is devoted to the pathogenesis and clinical course of the disease, not merely as it occurs in children, but as it is seen in primary form in adolescents.

Neither section is a mere review of accepted facts; each is distinctly individualistic, representing views championed particularly by its author. Miller is definitely committed to the view that tuberculosis of the adult represents endogenous infection almost exclusively. His statement that this is the contested, however, by many students of the disease. He follows the "trigger hypothesis" of Redeker in explaining the cases apparently resulting from view of the majority of clinicians and pathologists today would probably be contact with open disease. He divides tuberculosis into non-phthisical,

prephthysical and phthysical forms, and subdivides the latter into early, established and terminal pneumonic phthisis. As an advocate for the theory of endogenous onset of adult tuberculosis, he adopts the view that "there is no such thing as clinically definite incipency of pulmonary tuberculosis." The process is a continuous story, if not one of uniform speed. The various types of tuberculosis, which are well recognized by tuberculosis specialists in general under varying designation, are abundantly illustrated by excellent reproductions of Roentgen ray films. The section devoted to treatment is concise and practical, with the lines clearly drawn for management of cases of the different types and their various complications.

Wallgren's section is notable for its consideration of the clinical character of primary tuberculosis, a subject of much renewed interest in view of the world-wide postponement of first infection tuberculosis and the accompanying general diminishing mortality. Numerous case reports are included, and the relations to allergy and the development and waning of tuberculin sensitiveness are particularly stressed. Like Miller, Wallgren adopts the view of endogenous exacerbations as the cause of post-primary manifestations of tuberculosis. He is also a vigorous proponent of the importance of constitutional factors in resistance. His thesis of the genesis of the tuberculosis of adult life is concisely stated as follows: "A combination of a good natural resistance and the absence of unfavorable factors will prevent the occurrence of consumption. A combination of an inherited low resistance and unfavorable factors is almost inevitably bound to lead to phthisis."

All interested in tuberculosis will find the book stimulating and informative.

E. L.

NEW BOOKS.

The Genuine Works of Hippocrates. Translated from the Greek by FRANCIS ADAMS, LL.D., Surgeon. With an Introduction by EMERSON CROSBY KELLY, M.D. Pp. 384; 8 plates. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.00.

The Physiology and Pharmacology of the Pituitary Body. Vol. II. By H. B. VAN DYKE, Head of the Division of Pharmacology, Squibb Institute for Medical Research, New Brunswick, N. J.; Honorary Professor of Physiology, Rutgers University, etc. Pp. 402; 28 illustrations. Chicago: The University of Chicago Press, 1939. Price, \$4.50.

Physiology of the Uterus. With Clinical Correlations. By SAMUEL R. M. REYNOLDS, M.A., Ph.D., Fellow, John Simon Guggenheim Memorial Foundation, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y.; Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. With Forewords by GEORGE W. CORNER, M.D., Professor of Anatomy, University of Rochester School of Medicine and Dentistry, Rochester, and ROBERT T. FRANK, M.D., F.A.C.S., Consulting Gynecologist, Mt. Sinai Hospital, New York; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University, New York. Pp. 447; 44 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$7.50.

Enrico Bottini and Joseph Lister in the Method of Antisepsis. Pioneers of Antiseptic Era. By G. P. ARCIERI. (Reprint from *Almeone*, Vol. 1, No. 1, 1939.) Pp. 40; 1 illustration. New York: Franco Frusci, 1939.

The Patient as a Person. A Study of the Social Aspects of Illness. By G. CANBY ROBINSON, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. Pp. 423. New York: The Commonwealth Fund, 1939. Price, \$3.00.

Fever and Psychoses. A Study of the Literature and Current Opinion on the Effects of Fever on Certain Psychoses and Epilepsy. By GLADYS C. TERRY, Research Associate in Neurology, Neurological Institute of New York, Columbia University; Formerly Research Assistant in Psychiatry, Henry Phipps Clinic, Johns Hopkins University. Pp. 167. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.00.

Clinical Pathological Gynecology. By J. THORNWELL WITHERSPOON, B.S. (Princeton), B.A., and M.A. (Oxon.), M.D. (Johns Hopkins), Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Pp. 400; 271 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

Studies on the Changing Incidence of Peptic Ulcer of the Stomach and Duodenum. By GUNNAR ALSTED, M.D., Privat-docent at the University of Copenhagen; Assistant Physician and Member of the Staff, Bispebjerg Hospital, Copenhagen. With a Preface by PROFESSOR E. MEULENGRACHT. Pp. 148; 12 illustrations. Copenhagen: Ejnar Munksgaard, 1939. Price, Sh. 10/

End Results in the Treatment of Gastric Cancer. An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment. By EDWARD M. LIVINGSTON, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital, New York; Assistant Clinical Professor of Surgery, New York University College of Medicine, etc., and GEORGE T. PACK, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York City; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven, and Cornell University Medical College, New York City. With a Foreword by BOWMAN C. CROWELL, M.D., Associate Director, American College of Surgeons. Pp. 179; illustrated. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.00.

What it Means to be a Doctor. By DWIGHT ANDERSON. Pp. 87. New York: Medical Society of the State of New York, 1939. Price, \$1.00.

Vignettes of fictitious doctors aimed to give the prospective physician and the public better knowledge of what a physician's life consists of. Sponsored by the Medical Society of the State of New York and based on a questionnaire sent to 500 physicians in various fields, asking four questions calculated to illuminate the subject.

Le Radon en Thérapeutique. By DOCTEUR P. E. MORHARDT. Pp. 19. Paris: Édité Par Les Laboratoires Virac, 1939.

Rural Medicine. Proceedings of the Conference Held at Cooperstown, New York, October 7 and 8, 1938. Pp. 268; 15 illustrations, 13 tables and 35 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, \$3.50.

Proceedings of the American Philosophical Society for Promoting Useful Knowledge, held at Philadelphia (Vol. 80, No. 3, Feb. 10, 1939). Contents: Measles and Scarlet Fever in Providence, R. I., 1929-1934, with Respect to Age and Size of Family. By EDWIN B. WILSON, CONSTANCE BENNETT, MARGARET ALLEN and JANE WORCESTER, Harvard School of Public Health. Pp. 120; illustrated. Philadelphia: The American Philosophical Society, 1939. Price, 75c.

The Medical Clinics of North America, Vol. 23, No. 3 (New York Number, May, 1939). Pp. 277; 30 illustrations. Philadelphia: W. B. Saunders Company, 1939.

*Physiological Differentiation in *Lymnaea Columella*.* By JOSHUA L. BAILY, JR. With a Foreword by RAYMOND PEARL (The American Journal of Hygiene, Monographic Series, No. 14, April, 1939). Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 133; illustrated. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.00.

Life and Letters of Dr. William Beaumont. By JESSE S. MYER, A.B., M.D., Late Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, Bt., M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England. Pp. 327; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, \$5.00.

Heart Patients. Their Study and Care. By S. CALVIN SMITH, M.D., Sc.D., Formerly Special Heart Examiner for the Surgeon General's Office during the World War at home and abroad. Pp. 166. Philadelphia: Lea & Febiger, 1939. Price, \$2.00.

Problems in Prison Psychiatry. By J. G. WILSON, M.D., Senior Surgeon (Retired), United States Public Health Service; Director, Division of Hospitals and Mental Hygiene, Department of Health of the State of Kentucky, and M. J. PESCOR, M.D., Clinical Director, United States Public Health Service Hospital, Fort Worth, Texas. Pp. 275. Caldwell, Idaho: The Caxton Printer, Ltd., 1939. Price, \$3.00.

The New International Clinics, Vol. 2, N. S. 2, June, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. With 17 Collaborators. Pp. 321; many illustrations and 1 colored plate. Philadelphia: J. B. Lippincott Company, 1939.

This number includes several articles of important present interest such as Musser's Pellagra; Wilder's Diabetic Arteriosclerosis; Neurologic (Clough) and Psychiatric (E. L. Richards) Aspects of Vitamin Deficiencies; Choice of Methods for the Correction of Anemia (Wintrobe). There are 6 "Clinics" and a Review of Peroral Endoscopy by L. H. Clerf.

NEW EDITIONS.

Sex and Internal Secretions. A Survey of Recent Research. Editor: EDGAR ALLEN, Yale University. Associate Editors: CHARLES H. DANFORTH, Stanford University, and EDWARD A. DOISY, St. Louis University. Twenty-seven Contributors. With Forewords by ROBERT M. YERKES, Yale University. Pp. 1346; 454 illustrations, 2 color plates, and numerous tables. Second edition, enlarged and revised. Baltimore: The Williams & Wilkins Company, 1939. Price, \$12.00.

Recent Advances in Medicine. By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School, etc., and E. C. DODDS, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopaedic Hospital. Pp. 431; 42 illustrations. Ninth Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, \$5.00.

Food and Health. An Introduction to the Science of Nutrition. By A. BARBARA CALLOW, M.A. (CANTAB.), M.Sc. (LOND.), M.S. (YALE). Pp. 168; illustrated. Second Edition. New York: Oxford University Press, 1938. Price, \$1.75.

Textbook of General Surgery. By WARREN H. COLE, M.D., F.A.C.S., Professor of Surgery, University of Illinois College of Medicine, etc., and ROBERT ELMAN, M.D., Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Pp. 1031; 559 illustrations. Second Edition. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.00.

Laboratory Manual of the Massachusetts General Hospital. By FRANCIS T. HUNTER, M.D. Pp. 119. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$1.75.

PROGRESS OF MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF

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ADDISON'S DISEASE.

ALMOST 300 years passed from the time Eustachius discovered the adrenal glands in 1563 until Addison described the disease which now bears his name in 1849,^{1a} and again in 1855.^{1b} In the 75 years following Addison's description increasing recognition of the disease continued, but only in the past 10 years has the fundamental nature of the mechanisms involved in the symptom-complex begun to become apparent. Truly Addison's wish is in the process of being fulfilled, "I cannot but indulge the hope, that by attracting the attention and enlisting the co-operation of the Profession at large, they (the facts) may lead to the subject being properly examined and sifted, and the inquiry so extended, as to suggest, at least, some interesting physiological speculations, if not still more important practical indications." The literature on this subject has become so voluminous that only certain recent aspects of clinical interest find room for review here. Much of additional interest will be found in the Symposia on Quantitative Biology of the Cold Spring Harbor for 1937,³² where cortical hormones are discussed by many eminent authorities.

Etiology. The original description of Addison's disease rested upon the basis of tuberculosis of the adrenal gland. Subsequent reports have indicated that as high as 90 % of Addison's disease patients have tuberculosis of this organ, and considerable variation in this value has been reported. Guttman,²⁷ in his survey of the literature in 1930, found the causes in 566 cases to be tuberculosis in 69.72 %, atrophy in 19.38 %, amyloid in 1.73 %, neoplasm in 1.24 %. The remaining 7.83 % were divided among such diagnoses as hemorrhage, syphilis, pressure atrophy, fatty degeneration, venous thrombosis, and arterial emboli.

Less than one-half of those with Addison's disease due to tuberculosis show associated tuberculosis elsewhere,^{62a} and until recently such complicating lesions have been shown to have little effect on the course of the disease. The lungs are the focus in approximately 50 % and hidden or active foci in other parts of the body in the remainder. Tuberculosis of the adrenals is hematogenous and secondary to tuberculosis elsewhere.

The incidence of Addison's disease is surprisingly low in sanatorium patients. In 15 years one group¹³ found only 2 cases in 4500 patients. The explanation is questionable, but probably involves many factors. Extensive bilateral tuberculosis of the adrenal glands is usually seen in cases with minimal or healed pulmonary tuberculosis. Furthermore, extensive disease of the adrenal glands often appears after dismissal from sanatorium care. It must be remembered, too, that pulmonary tuberculosis may mask Addison's disease, for it may produce similar symptoms. Still, under these circumstances Bronfin and Guttman have shown that the diagnosis may be made when asthenia, loss of weight, anorexia, and abdominal distress are out of proportion to the extent or activity of the pulmonary lesions.

Sex distribution in tuberculous Addison's disease has varied from equal values to an incidence favoring males. Age incidence follows closely the death age distribution of tuberculosis in general. It is uncommon in childhood,²² only from 1 % to approximately 3.5 % of the cases occurring in this period.

Tuberculosis of the adrenal glands is not always accompanied by Addison's disease, even when bilateral. Colton¹⁵ found only 6 cases of Addison's disease in 14 patients with bilateral tuberculous adrenals.

Next to tuberculosis, atrophy is the most frequent cause of Addison's disease, and its incidence appears to be increasing.⁶⁹ Of 18 patients with Addison's disease, 11 were found to be due to tuberculosis and 7 to atrophy. Susman, in his review of 11 reports from various countries, found support of these figures in certain geographical areas. Highest incidence of atrophy occurred in the English group. Of the 189 cases of Addison's disease, 96 (51 %) were from England. Thirty-two (70 %) of 46 instances of atrophy were in the English group, an incidence of 33 % among the English cases. American reports, too, continue to show an increased incidence of atrophy. Von Glahn⁷⁷ saw, from 1926 to 1935, 5 instances of atrophy, while in 24 years previously he had seen only 6 cases, all due to tuberculosis. Barker,⁷ in 1929, reported 28 cases, 25 due to tuberculosis and 3 to atrophy. Robertson⁵⁵ indicated that since Barker's paper, 19 cases were observed, 9 (approximately $\frac{1}{2}$) due to atrophy.

Atrophy, unlike tuberculosis, has been more frequent in females,⁶⁹ and it, too, has been found in children. (It is rare in childhood.^{5,22,39,64} Atkinson has reviewed the subject thoroughly and has collected all reported cases of all types.) The usual age incidence is between 25 and 60 years, and the general incidence in available autopsy series varies from 0.025 to 0.29 %.

The etiology of so-called atrophy is still a mystery, despite the many, and often divergent, views offered as an explanation.¹¹ A partial list of suggestions includes congenital hypoplasia, endocrine factors, chronic inflammations (such as lues, tuberculosis, and non-specific inflammations), circulating cytotoxins, and simple atrophy. These many explanations have led to a number of different names being applied to the condition,⁷⁸ such as simple atrophy (Karakaschaff), idiopathic atrophy (Simmonds), inflammatory granular atrophy (Rössle), cytotoxic contracted suprarenal gland (Kovacs), and chronic idiopathic (primary) suprarenal insufficiency (Bittorf).

In atrophy, as well as in tuberculosis, much controversy has arisen in the past concerning the place and importance of the medulla in the etiology of the clinical picture. Recent work, including substitution therapy in animals and man, indicates the prime importance of the cortex, but does not deny that medullary changes may contribute to the clinical picture in any one patient.

Endocrine influences from glands other than the adrenal have enjoyed considerable popularity as an explanation of the etiology of atrophy, particularly since interrelationships of endocrine glands, including the adrenal, have been definitely accepted. Chief interest centers around the thyroid and the pituitary. The problem of the participation of the thyroid has prompted spirited debate in the German literature,⁷⁸ for the thyroid quite frequently shows lymphocytic infiltration which may become very extensive. The significance of this change is unknown. While evidence of hyperactivity of the thyroid is found in some cases, it is not a constant finding.¹⁶

Recently the pituitary has received much attention in relationship to Addison's disease. Nicholson⁵¹ autopsied 25 adrenalectomized dogs and compared the anterior pituitary with the glands of normal animals. He was unable to find histologic differences. In sections from 7 pituitaries from human Addison's disease, there was a reduction in the number of basophils, along with abnormal basophilic cells only in those patients with adrenal cortical atrophy. From such findings he suggested that Addison's disease due to atrophy begins primarily in the anterior lobe of the pituitary, and that the absence of adrenotropic hormone causes adrenal cortical atrophy which, in turn, is responsible for the clinical picture of Addison's disease.

The work of others does not warrant such suggestions. In 1935 Croke and Russell¹⁶ pointed out that in 9 of 13 published examinations of the pituitary gland in Addison's disease a diminution of basophilic cells is described. A great reduction of basophilic cells was constant in their series of 12 cases, whether or not the adrenals were tuberculous or atrophied, a factor against Nicholson's view. They found large chromophobe cells, a decrease in the number of acidophils, and a number of abnormal transitional basophils, with a constant striking reduction in the number of ripe basophils. In 5 glands the findings were checked by Rasmussen's method. The abnormal basophilic cells were more numerous than the ripe basophils, but both groups together were below the minimum for ripe basophilic cells in Rasmussen's series, except in one case.

Discussing these observations, the authors recall that basophilic adenomata of the pituitary are frequently accompanied by diffuse hypertrophy of the adrenal cortex, the opposite findings of Addison's disease. Likewise, destruction of the anterior lobe of the pituitary^{54,61} is followed by adrenal cortical atrophy. Such atrophy is not associated with cellular infiltration or fibrosis. Atrophy of Addison's disease is not simple atrophy but a destruction of the parenchyma similar to that of acute atrophy of the liver, and areas where cells disappear are infiltrated with large and small lymphocytes, plasma cells, and monocytes. The remaining cortical cells show changes in staining reaction, are hypertrophied and are grouped. Later fibrosis appears. These authors, therefore, consider the atrophy of Addison's disease a destructive

atrophy, differing from that secondary to pituitary hypofunction. The diminution in basophils may be secondary to it, for although Nicholson found no differences in adrenalectomized dogs, others⁵⁰ have found definite changes in rats.

Bloch¹⁰ has advanced the theory that atrophy is not true atrophy but the result of a perversion of the normal process of development of the medulla during fetal life. Normally the embryonic neurocytes, which migrate through the cortex, eventually form the medulla. With the increase in size of the medulla there is a corresponding atrophy of the cortical inner zone with a regeneration of the glomerular zone. Bloch thinks, if the process of atrophy of the inner zone is prolonged into early childhood or later life, the great bulk of the cortex may eventually disappear, having been replaced by embryonic neurocytes. This theory has received little support.

Other possibilities have been considered in the cause of cortical necrosis. Wells, Humphreys and Work⁷⁹ have noted in the cortical lesions histologic features similar to those of cinchophen poisoning in the liver. This, together with the similarity of the appearance of both diseases in hospitals during recent years, aroused their suspicions that the selective destruction might have been produced by some drug or other chemical agent. Microscopic lesions in the necrotic adrenal cortex of a patient who had taken germanin were similar to those seen in Addison's disease. The picture was reproduced in animals. However, this chemical has not been related to cortical atrophy in patients with Addison's disease. The report merely indicates, indirectly, that drugs may be responsible for the atrophic cortex in human Addison's disease, without offering any confirmation of this hypothesis.

Less common causes of Addison's disease continue to be reported and new and unusual associations with Addison's disease appear to be limited only by the number of conditions capable of causing sufficient cortical dysfunction. For example, a French report⁴¹ describes Addison's disease secondary to a destructive lesion of the splanchnic medullary centers. Somewhat similar is Rogoff's patient,^{56b} who suffered from diabetes mellitus. An attempt was made to benefit the diabetes by denervation of the adrenals. Both sides were denervated, but at different times. Addison's disease developed, the surgical manipulations apparently resulting in occlusion of blood-vessels and degeneration of the adrenal cortex. The latter inference is based upon animal studies in which creation of serious local circulatory disturbances produced acute and chronic adrenal cortical insufficiency.^{56a} Snell, Wilder and Cragg⁶³ have reported a similar case with adrenal atrophy following denervation resulting in a typical clinical picture of Addison's disease. This complication of adrenal surgery must be rare, however, when one considers the frequency of such surgery and the rarity of reports of the development of Addison's disease.

Tuberculosis may be an indirect as well as a direct cause of Addison's disease by the production of amyloid degeneration. Such changes are not frequent. Guttman²⁷ found an incidence of only 1.26%. Yet amyloid is found in the adrenals, if sought, in many cases of amyloidosis of the spleen and other organs. For example, in 100 patients with tuberculosis, 18 instances of amyloidosis were found, 14 of which (78%) showed amyloid in the adrenals.¹³ The suggestion was made that at

least 3 possibilities may account for the differences in the incidence of amyloidosis of the adrenal and Addison's disease due to amyloidosis; namely, insufficient destruction of cortex, prevention of Addison's disease by the medulla, and masking of the symptoms by pulmonary tuberculosis. The effect of the medulla is questionable for it is well preserved. Cortical tissue is preserved in amyloidosis of the adrenals and islands of tissue appear normal histologically. In Bronfin and Guttman's 14 cases, histologic changes in the adrenal seemed to show a relationship between the extent of the amyloid of the cortex and the symptoms. They also call attention to the possibility that in advanced pulmonary tuberculosis there are symptoms of Addison's disease which are usually unrecognized and attributed to existing tuberculosis.

Weiner⁷⁸ described a patient with nuclear inclusions in the adrenal cortical tissues but not in the other tissues sectioned nor in many adrenals of varied diseases. Aside from the nuclear inclusion bodies the findings in this patient fit other descriptions of atrophy.

Addison's disease occurs at times in association with other diseases, and frequently attempts are made to show interrelationships and common etiologic factors. For example, pellagra has occurred with Addison's disease.⁵⁹ Attention has been called to the similarity of the pigmentary phenomena in the 2 diseases. Similarly, Addison's disease has been reported in a patient with Buerger's disease.⁶⁰ No causative relationships between the 2 conditions were established, and the possibility of adrenal atrophy resulting from circulatory changes due to the Buerger's disease was discarded as unlikely in this patient. Addison's disease has also been reported in association with mycosis fungoides.⁴

Attempts have been made to show hereditary factors in Addison's disease. At present such associations seem unimportant. Familial occurrence of acromegaly and Addison's disease has been reported,⁴⁷ and the disease is usually considered less frequent in the negro. Flippin and Smith²⁰ brought this out strikingly in their report. They point out that since Addison's disease occurs more frequently in the laboring class, and since tuberculosis is very frequent in the negro, one would expect a high incidence of Addison's disease in this group. Yet it is very infrequently reported in the negro, though it is probably more frequent than is generally appreciated. The normal pigmentation of the negro may be a factor in the failure of its recognition, although in 14 reported cases there were 12 with increasing pigmentation recognized by the patients or their friends.

Clinical Aspects. Only certain aspects of the clinical expressions of Addison's disease will be considered here. The usual course of the clinical findings, pigmentation, asthenia, blood pressure variations, gastrointestinal and other well known changes will be passed over without comment. The average duration of symptoms, and life, is said to be 1 to 3 years, longer with atrophy than with tuberculosis, and longer with marked pigmentation than without it. Of chief importance is the division of these symptoms and signs into 2 groups, one the chronic findings, such as slight asthenia, pigmentation, symptoms of hypoglycemia and hypotension; the other the findings of crisis, such as anorexia, nausea and vomiting, diarrhea, and circulatory collapse. This classification is similar to that used in diabetes mellitus and exophthalmic goiter.

Since the clinical picture results from an insufficient supply of cortical

hormone or hormones, recitation of the clinical aspects is essentially an exposition of the functions of the cortical hormones, and, to quote Loeb,^{43b} until it is available in large amounts in crystalline form, the functions will remain shrouded in mystery and confusion. A discussion of the hormones, other than cortin, may be found in the report of Hartman.³² Recent production of synthetic preparations having the life sustaining activity of cortical extract⁶⁷ indicates that we may be on the verge of a clarification of this problem.

Changes in carbohydrate metabolism have been noted both in patients and in experimental animals. Removal of the adrenal glands in animals and the development of Addison's disease in certain patients results in a decreased blood sugar and an increased sensitivity to insulin. Adrenalectomized animals with resulting adrenal insufficiency have been shown to have a reduced liver glycogen and a low blood sugar^{12b} and have lost the ability to form liver glycogen from injected glucose. Welty and Robertson⁶⁰ have recently reviewed the clinical aspects of hypoglycemia.

Hypoglycemia has not been found in all patients with Addison's disease. In some it may be marked, however, producing coma. For example, Anderson and Lyall's patient³ died in coma with hypoglycemia while plasma chlorides and blood urea were both within normal limits. It has been attributed to disturbances of cortical function,^{12a,b} to possible deficiency of basophilic cells in the anterior pituitary¹⁶ and also to destruction of the medulla with a disturbance in the balance between insulin and adrenalin. There is evidence¹⁴ that blood adrenalin is lowered in Addison's disease, a sign thought by certain European investigators to be of value in atypical and abortive cases. Further evidence for medullary involvement is the demonstration by Harrop and Weinstein²⁹ that insulin sensitivity persists in adrenalectomized dogs with adequate dosage of cortical extract. Varying involvement of the medulla would explain the presence of hypoglycemia in some patients and its absence in others. Still there may be more than a single mechanism, for Althausen, Anderson and Stockholm² have recently demonstrated a reduced absorption of glucose from the intestine, corrected by salt therapy, in experimental adrenal insufficiency. Possibly both the medulla and cortex play a part in patients.

In one of Welty and Robertson's patients the symptoms of increased sugar tolerance overshadowed those of the destructive adrenal lesion and made differential diagnosis very difficult. They believe that with the symptoms of hypoglycemia, Addison's disease should always be considered in the differential diagnosis. Hyperinsulinism and Simmonds' disease may be difficult to rule out. In hyperinsulinism, pigmentation and blood pressure changes are absent and the glucose tolerance curves differ. In Addison's disease the curve is relatively flat; it does not decrease rapidly; and shock is rare without complications. Simmonds' disease is rare, the glucose tolerance curve may simulate that of Addison's disease, but clinical features help in differentiation.

The changes in blood electrolytes in Addison's disease are most interesting. The work of Loeb and his associates^{43a,44} and of Harrop and his co-workers^{30,31} is well known and will be summarized only briefly here. Loeb noted that the symptoms of Addisonian crisis, nausea and vomiting, increased pulse rate with falling blood pressure, severe pros-

tration, weakness, dehydration and shock resembled the picture seen with depletion of inorganic base in diabetic acidosis, cholera, diarrheas of infancy, and high intestinal obstruction. He studied, in detail, the blood electrolytes both in adrenalectomized animals and in patients with Addison's disease, and found decreases in total base entirely at the expense of sodium. There was an increase in the hematocrit readings indicating a decrease in water content of the blood, a decrease in bicarbonate or chloride content of the serum, or both. When changes developed rapidly, blood urea increased before oliguria and anuria developed. These changes accompanied an actual increased loss of sodium through the kidneys and enough sodium was excreted to indicate a loss from interstitial fluid as well as from the blood. Urinary chlorides and volume increased as well as urinary sodium. Chloride changes paralleled those of sodium but were not as great.

These findings have been confirmed by Harrop and his group.³⁰ In permitting adrenalectomized dogs, maintained on cortical extract, to go into crisis they demonstrated a shock-like syndrome produced by loss of body fluids. The findings, in sequence, were progressive hemoconcentration, loss of weight, anorexia, lowered body temperature, lowered oxygen consumption, muscular weakness, vomiting, diarrhea, with ultimate failure of the circulation manifested in diminished blood flow and reduced blood pressure. Blood urea rose and plasma chlorides and plasma total base fell at the expense of sodium. Blood magnesium and potassium rose. Harrop, however, has shown no appreciable loss in the water content of liver and muscle tissue.

A number of explanations for these changes have been offered.⁴⁴ Were some organic acid to take out fixed base as in diabetic acidosis, ammonia production would increase. It has been reported as reduced. If sodium loss were due to water loss, one could not account for the fact that sodium loss exceeds water loss. Likewise, with primary water loss, blood sodium would rise rather than fall. The most likely explanation is the regulation of sodium metabolism by the cortex. The high blood potassium has also led to the view that disturbed metabolism of this element is the basic fault.⁸⁴ Zwemer and Truszkowski found that maintenance of high blood potassium levels in normal animals produced symptoms similar to those of adrenal insufficiency. They believe that regulation of potassium metabolism is an important function of the adrenal cortex and that symptoms of crisis may be considered secondary to the rise in potassium. At any rate, the above findings^{31b} make unnecessary the assumption that the suprarenal cortex or its hormones has a detoxifying action on some product of metabolism. They show that the process involved is essentially shock associated with progressive loss of plasma volume, lowered general metabolism and blood flow as well as later lowering of body temperature and blood pressure. Hemoconcentration is thus said to produce circulatory collapse and explains loss of weight, lowered body temperature, anorexia, diarrhea, and vomiting. It is of interest that, in pituitary basophilism with adrenal cortical hyperplasia, the electrolyte pattern has shown, in most respects, diametrically opposite findings.⁴⁶

It must be recalled, as will be stated below under "Diagnosis" that reduced blood sodium does not necessarily indicate the presence of

Addison's disease, for a number of other conditions will also produce this change.

At first there was considerable difference of opinion as to the mechanism of the hemoconcentration and the nature of the shock picture. Loeb's findings, that fluids are lost from the body, have already been stated. These have been confirmed many times. He stated further^{43b} that in certain instances loss of base and water does not appear great enough to produce the profound peripheral circulatory collapse encountered, and suggested that there may be some regulatory control of the vascular bed directly. Swingle and his associates^{71,72} were unable to account for the dehydration and the associated changes in experimental adrenal insufficiency on the amount of fluid lost as urine, suggesting a mechanism similar to histamine shock. Collapse and hemoconcentration have been observed⁷⁰ in adrenalectomized dogs, following withdrawal of cortin, without loss of sodium, chloride, or water in the urine, and the symptoms have been relieved with cortin alone; still a reduction in the amount of interstitial fluid has been shown.²⁸ Swingle and his associates felt that the relief they obtained resulted from mobilization of intracellular fluids and electrolytes. Harrop offers a similar suggestion and states that blood concentration in adrenal insufficiency may be due to 3 factors: 1, the movement of extracellular fluid to tissue cells; 2, drainage of plasma water into extracellular fluid; and 3, an increased urinary output. He feels the first is the most important.

Most interesting, in the light of the above findings, is a recent report by Hartman and his associates.³⁴ They have demonstrated that the factor which causes retention of sodium in normal animals can be separated from the vital factor, cortin, by repeated extractions with ethyl ether. The cortin content of the extract was assayed on adrenalectomized cats; the presence of the sodium factor by the effect on sodium retention in normal dogs. They have made many preparations with a high cortin content but no sodium-retaining power. Adrenalectomized cats have been maintained in good condition with no significant weight changes with plasma sodium levels characteristic of untreated animals in an advanced stage of insufficiency. Reduction of cortin to the point of insufficiency produced little change in the plasma sodium while addition of the sodium factor caused a rise of plasma sodium to normal levels. The inability of the sodium factor to maintain both adrenalectomized cats and dogs was demonstrated.

They interpret the evidence as indicating a separate adrenal hormone responsible for sodium retention. In the absence of this hormone cortin maintains the adrenalectomized animal in spite of the diminished plasma sodium. These findings bring up many interesting problems, and if confirmed, will change considerably present views of cortical hormone function.

The elevation in blood urea suggests that renal function may be impaired in Addison's disease, particularly since removal of the glands from animals has also resulted in reduction in P.S.P. excretion.⁴⁹ Urea clearance is also diminished,^{43b,66} and since these changes occur after omission of cortical extract in adrenalectomized animals, it is considered cortical in origin. Salt therapy, as well as cortical extract, tends to bring these three changes back to normal. Loeb lists the following as evidences of alteration in renal function from lack of cortical hormone:

1, elevation of blood urea, creatinine, phosphates, and sulphates; 2, diminished urea clearance; 3, reduced excretion of P.S.P.; and, 4, increased sodium excretion. To this may be added potassium retention, but whether this represents a manifestation of disturbed renal function or a more general disturbance of potassium exchange is not known.

More recently Willson and Sunderman⁸² have shown in a patient with Addison's disease on restricted water intake a retention of sodium and chloride and a reduced urea clearance during the period of oliguria. Simple restriction of water resulted in symptoms of severe adrenal insufficiency. They believe these changes must be the result of the failure of the adrenals alone, for no coincidental renal disease was found. Swingle and his associates⁷¹ found in adrenalectomized dogs an inverse relation of the blood urea nitrogen to the blood pressure. Elevation of urea nitrogen occurred simultaneously with the fall in arterial pressure and did not precede it. They think that the azotemia is probably extrarenal in origin and may have no necessary relation to the kidney. It is also possible that impaired circulation through the kidney may account for reduction in P.S.P. excretion and reduced urea clearance.

The exact mechanism of many of the findings of Addison's disease is not known. The relationships of the changes in blood volume, dehydration, and so forth, to hypotension, gastro-intestinal disturbances, weakness, and other findings has already been given. Loeb has pointed out that oxygen consumption is not affected until 4 days after the withdrawal of maintenance cortical extract in animals and suggests it may be secondary to the dehydration. The mechanism of neurologic findings, such as confusion, disorientation, aphasia, reflex changes, and convulsions of acute insufficiency is not understood. Neurologic changes have been ascribed to hypoglycemia and at times result from this change. However, they do occur in the absence of hypoglycemia and may result^{43b} from decreased cerebral circulation as a part of the more general picture of dehydration and shock.

Infection may precipitate crisis and appears to affect cortical function as it does the islet function in diabetes.

There is a large literature upon the possible effects of cortical function on immune reactions. This will not be reviewed here.

There is little definite information concerning the genesis of the pigmentary changes in Addison's disease. It is not always present and is reported both as lessening with treatment with salt and cortical extract, and as being unchanged.^{31a, 81c} Wilkinson's patients showed a marked disappearance of pigmentation from the mucous membranes, but not from the skin. Harrop found that treatment may slowly lessen the pigmentation of the skin, as did Wilkinson. He ascribed the change to a cessation of excessive deposits and mechanical wearing away of the outer layer where pigment is deposited. Some feel that the rather sudden lessening of pigmentation in several days following recovery from crisis is due to rehydration and its effects on the appearance of the skin rather than to actual change in pigmentation itself. This is further suggested by a rapid return of the color if the patient again goes into crisis.

The pigmentary changes may be related in some way to vitamin C metabolism. This brings up the possible relation of vitamin C to cortical function. It is well known that the middle zone of the cortex contains

large quantities of vitamin C and it has even been suggested that the adrenal gland may synthesize this vitamin. Flowers and Young²¹ feel that, with a greater concentration of vitamin C in the adrenal cortex than in any other tissue except, perhaps, the pituitary, one can hardly assume it is just stored there, because of the small size of the area and the great daily excretion. They believe it more logical that vitamin C has an integral part in the function of the cortex. Vitamin C is a reducing agent. They state further that perhaps the pigmentation is explainable as a result of vitamin C deficiency associated with the skin oxydase reaction, for melanin is composed of a benzene ring base and can be produced by oxidation of tyrosine. Reduction of tyrosine leads to adrenalin. Since little adrenalin is said to circulate in the blood of these patients it seems plausible to them that some of the ingested tyrosine has been converted into melanin because the body can no longer convert it into adrenalin. These considerations are purely theoretical. However, low blood cevitamic acid levels are found in patients with Addison's disease whether or not it is due to failure of the adrenal glands to participate in vitamin C metabolism. Patients are said²¹ to grow worse when vitamin C is withdrawn from the diet.

Other observations lend some weight to the participation either of vitamin C in cortical function or of cortical function in vitamin C metabolism. A deficient mechanism for storage of vitamin C has been demonstrated in adrenal insufficiency.²⁴ Wilkinson^{81a} found that the degree of subnutrition paralleled the severity of the disease, which other patients in a low state of health did not show. He discards low intestinal absorption as a factor, for gastro-intestinal symptoms were under control in his patients who also responded to oral cevitamic acid. Increased need or destruction of the vitamin is more likely in a febrile disease than in a disease with subnormal temperature and metabolism. He, too, considers, from the richness of the gland in vitamin C that it may have a function in the oxidation-reduction potentials in the adrenals and would thus serve to stabilize adrenalin and cortin. Vars and Piffner,⁷⁵ from work in dogs, state that if the adrenals play any rôle in the metabolism of vitamin C, it is conferred by the adrenal cortical hormone. Finally, Wilkinson, as did Flowers and Young, suggested that cevitamic acid may be concerned with the regulation of pigmentation of the skin. It is known to inhibit pigment formation *in vitro*, and Hoff³⁷ has reported alleviation of pathologic pigmentation in scurvy and Addison's disease by its use. Others have reported relief of marked pigmentation by cevitamic acid therapy.⁵⁸

The possible relationships of other vitamins, particularly the B group to the adrenal gland has been discussed by Hartman.³²

Cardiac mechanismal disturbances have been noted by electrocardiography in Addison's disease.¹⁸

Diagnosis. Diagnosis in Addison's disease may be simple when the cardinal symptoms are present. Pigmentation is almost essential to definite diagnosis by bedside methods alone, for other features of the disease are common in other conditions. The pigmentation varies, but Snell^{62b} has recounted certain characteristics which are helpful in diagnosis. It is most pronounced on exposed surfaces, is diffuse, and is accentuated at pressure points and scars. Freckles, black and minute, are often noted on the neck and shoulders. The genitals, anus, axillæ,

nipples, and lips show accentuation of pigmentation. The oral mucous membranes are involved. The dorsum of the hand may be darker than the palm with a well defined line of demarcation. Biopsy shows only increased melanin. In less clear cut and atypical cases, diagnosis may be difficult and may require the use of special procedures.

The special procedures of value used in diagnosis may be divided into 2 groups: 1, attempts to precipitate crisis, or the electrolytic changes accompanying crisis; and, 2, attempts to relieve symptoms or changes in blood chemistry by the use of cortical extract. The first group consists of several well recognized procedures. The demonstration of sodium disturbances in Addison's disease quickly led to the introduction of the salt deprivation test, or salt-free diet, in diagnosis, particularly since blood sodium levels may be low in conditions other than Addison's disease and Addison's disease may occur with normal blood sodium levels. Withdrawal of salt may precipitate crisis, and in doubtful cases is of definite value.^{31a} Signs of relapse may occur as early as the second day, but as a rule 4 to 5 days are necessary. The blood sodium may drop rapidly as compared to that of patients with other diseases, regardless of the initial values.⁴¹ Patients with normal cortical function show no appreciable changes in blood electrolytes. The test is not infallible, and Johnson³⁸ has described a patient, later autopsied and found to have atrophy of the adrenal cortex, who, on a diet containing only 1.5 gm. daily of sodium chloride for 21 days, failed to show any change in plasma chlorides and urea nitrogen. When the test is used, patients must be closely watched for symptoms of crisis, and means of combating crisis, including intravenous salt and glucose solution and cortical extract, must be on hand for emergency treatment. Patients have died suddenly during or after the test.⁴²

The dangers and obvious restrictions of the salt deprivation test have led to the development of other procedures in diagnosis, involving control of the potassium intake. In 1931 Hastings and Compere³⁵ associated increased blood potassium with adrenal insufficiency. Loeb found similar changes in the blood potassium. Zwemer and Truszkowski⁸⁴ produced death in a few hours by administration of potassium to the adrenalectomized cat. Then, in 1937, Nilson⁵² precipitated crises in adrenalectomized dogs maintained on low potassium, low sodium diets by feeding potassium. This led to the application of methods of potassium control to diagnosis in man.

Cutler, Power, and Wilder^{17a,b} undertook to devise a standard test of the rate of excretion of sodium and chloride as a diagnostic index. They formulated a 3-day examination. On the day preceding the first day of the test, the patients received a general diet with no added salt. Then the test was begun with a diet including 0.95 gm. Cl ion, 0.59 gm. Na ion and 4.1 gm. of potassium. Fluid intake was controlled, and measured quantities of potassium given on the first and second days. Blood and urine samples were collected at stated intervals. It was found that the concentration of chloride in the urine of the third morning was diagnostically more significant than the volume of urine, the potassium concentration of the urine and the total excretion of the various ions. If the concentration of chloride in this specimen exceeds 225 mg. %, Addison's disease is strongly suggested; if less than 125, it is unlikely. The test has been found useful by others.⁴⁵ It exposes the patient with

Addison's disease to less risk of collapse than further salt restriction, but is not without danger. Cortical extract and intravenous glucose and saline solution must be kept on hand for emergency purposes and should be administered at the end of the test if Addison's disease is suspected. Further study is necessary to evaluate this test both as to its usefulness and its specificity, for Greene and Levine²⁶ have obtained altered potassium tolerance curves in a variety of conditions. The only chemical determination necessary with the test is the relatively simple chloride determination.

Tests involving administration of cortical extract remove the danger of precipitation of crisis, but, when based on objective data, involve extensive chemical determinations. One cannot depend upon the presence or absence of subjective improvement following the administration of cortical extract, as Kline⁴⁰ has pointed out. Kline's patient, who had a negative salt restriction test, improved markedly on injections of distilled water. However, objective changes produced by cortin may be used in diagnosis. Thorn, Garbutt, Hitchcock, and Hartman^{74a} have shown that daily cortin injections equivalent to the daily requirement of a severe case of Addison's disease produce only slight effects on the electrolytic balance of normal human subjects, although it is possible^{74b} to obtain measurable effects if sufficiently large amounts of hormone are used. With doses used in treatment, a positive effect of cortin on sodium and chloride balance of a patient suspected of Addison's disease makes the diagnosis more likely. In females, variations in electrolytes may occur at or near the catamenia, and must be taken into consideration.

Changes in dextrose tolerance and low fasting blood sugar often occur in Addison's disease, as does increased sensitivity to insulin. However, these changes occur in other conditions. Demonstration of calcification of the adrenals by Roentgen ray examination is very helpful if present, and in Snell's hands has been pathognomonic.

Treatment. Thorn⁷³ has recently reviewed adrenal cortical hormone therapy in these columns and little in addition need be said here. The reader is referred to his excellent review, which contains, as well, a discussion of sodium chloride therapy, and the use of the newer synthetic hormone preparation, desoxycorticosterone acetate.

It is only in the past decade that satisfactory cortical extracts have been available and the relationship of salt metabolism to cortical function studied in detail. Hence the two strongholds of treatment, hormone and salt, are relatively recent in their development. Cortical extracts have been used as far back as 1896, when Osler reported good results in one patient with an oral glycerine extract,⁵³ but their use was not satisfactory until about 1930. Also salt therapy was known to benefit adrenalectomized animals as early as 1925-1927^{8,48,68} but it remained for Loeb to demonstrate its effectiveness in therapy in 1933. In the meantime, changes in potassium concentration in the blood and urine had been demonstrated,^{35,43a} and, following Nilson's demonstration⁵² in 1937 that crises could be precipitated in adrenalectomized animals by its administration, the low potassium diet has been added to the therapeutic armamentarium.

There are several reports outlining the details of the handling of patients with Addison's disease, and for detailed management, the reader

is referred to the original reports.^{57,65,81b,c} Treatment may be resolved into two phases, treatment of the chronic or latent stage, and treatment of the crisis. Both involve the use of general measures, such as bed rest until stabilization of the blood chemistry is reached, warmth, and dietary measures, including high carbohydrate, adequate vitamin C content, and at times control of the potassium content. Directions for the preparation of low potassium diets are now available.⁷⁶ Treatment of underlying disease, if present, and avoidance of factors which may precipitate crisis, such as infection, overexertion, and exposure to cold are important. More specific measures, important in both stages of the disease, include salt and hormone therapy, and in crisis the treatment of dehydration.

Details of the handling of the patient in crisis have been outlined in the excellent paper by Rynearson.⁵⁷ During the early period of treatment the patient needs quiet and complete rest, large doses of cortical extract, up to 50 cc. daily, given in divided doses, parenteral fluids containing glucose, sodium, chloride and little or no potassium. Fluids are given by mouth when they can be taken and these are also fortified with sodium salts. Fluids and cortical extract are continued in large doses until symptoms and the blood chemistry, especially urea and chlorides, indicate a return to normal. This may be 2 to 3 days or longer. With a response the symptoms and signs disappear, metabolism, if depressed, rises, and blood urea and other constituents return to normal. Appetite returns and the weight begins to rise. Cortical extract is then reduced until a maintenance level is reached. This usually ranges from 1 to 5 cc.⁶⁵ and at times it may be stopped altogether with a high sodium diet.

In the chronic stage of the disease there is a wide variation in the measures necessary to keep the patient controlled. Some, apparently with considerable functioning cortical tissue may require only salt therapy. As high as 2 to 3 gm. 6 times daily may be given in milk or capsules. Such doses are often emetic and must be reduced. At times a mixture of sodium salts, sodium chloride, sodium bicarbonate, and sodium citrate, may be tolerated better. Chloride must always be given for chloride deficiency exists.

If added sodium salts alone are insufficient to support the patient, reduction of potassium intake may keep the patient symptom-free. In patients treated for crisis it may be possible later to eliminate completely cortical extract or reduce the dosage by this means. The great value of salt therapy in the chronic stage lies in its ability to lower hormone requirements and reduce the cost of treatment.

With complications, such as the common cold, or in the presence of pulmonary tuberculosis, cortical extract may be necessary, if not used before, or the dosage may be increased. Many patients without obvious complications require cortical extract for control. A number of factors, such as infection, the type of adrenal lesion, the "irreversible state," and extra-adrenal disease, may modify the response to cortical extract.

Modern treatment has added much to the usefulness of the patient, but frequently little to his life expectancy.²⁵ It has definitely prolonged life in a limited group. Patients feel well. They survive hot weather, infections and operations, and can lead an active life.

All patients do not react favorably to treatment⁹ even when the blood

chemistry returns to normal.⁵⁷ This may be related in some way to the demonstration of Hartman and his associates that the principal essential to life may be separated from the fraction controlling blood chemistry. At times patients return to crisis and large doses of extract fail to produce remission, the so-called "irreversible condition."³³

Complications of an endocrine nature from injections of cortical extract are rare. Edwards, Shimkin, and Shaver¹⁹ found hypertrophy of the breast in a man due to injections of cortical extract, and were unable to find a similar case in the literature. The gynecomastia subsided with omission of the extract and recurred when the extract was resumed.

Many attempts have been made, both in animals and in man to treat Addison's disease with adrenal grafts.^{6,23,36,83} Results, when suggestive of improvement, have all been questionable in patients.

Snell^{62a} has pointed out that the number of patients with Addison's disease and tuberculosis who will live long enough for tuberculosis elsewhere in the body to become a menace is increasing, due to present methods of treatment. He believes that the old view, that tuberculosis has no effect on the duration of life in Addison's disease, may have to be revised and treatment for tuberculosis, both medical, and surgical, will form an essential part of the treatment of increasing numbers of these patients.

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PEDIATRICS.

UNDER THE CHARGE OF
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DISEASES OF THE KIDNEYS IN INFANCY AND CHILDHOOD.

NORMALLY at birth the urologic system has been fully developed for some time, although it does not actually assume its functional responsibilities until after the connection with the maternal circulation has been lost. Congenital anomalies of the kidney occur and references to these are frequent in the literature. It is to be noted that the effects of these abnormalities are not always present in the neonatal period

nor even during the first year or two of life. Lazarus¹⁹ stated that polycystic disease of the kidney is characterized by the formation of cysts within the renal parenchyma due to congenital occlusion of portions of the renal tubular system. He pointed out that in spite of the fact that this disease is congenital, symptoms rarely appear before the fourth decade with the greatest incidence occurring between the ages of 50 and 60, with both sexes equally affected.

Steinberg³¹ reported a case of a congenital cyst of the kidney found in a newborn infant. He commented that the old idea that congenital and acquired cysts of the kidney are separate entities has been dispelled since the time of Küster, who was the first to believe that these cysts are present during fetal life. If the child went throughout life with this anomaly, it was probably one that had not progressed very far during the child's intrauterine life. However, if the condition had progressed to any extent, the child died during its fetal existence. The case that Steinberg reported was one in which hydronephrosis was found at birth with polycystic formation in the kidney.

Karsner's¹⁸ reported case of congenital nephritis is of interest not only because of its rarity, but because of its suggestion along the line of etiology of nephritis. While infection and the presence in the body of some fairly well-defined irritant are generally conceded as causes of nephritis, the occurrence of this disease in the newborn child of an apparently healthy woman leads one to think that this finely constructed gland may be susceptible to the irritation of many substances of which little is known.

According to Fullerton,¹⁵ Henry Morris classified cysts of the kidneys as follows: 1, the small and numerous cysts which occur in granular kidneys and which are of pathologic rather than of clinical importance; 2, dermoid cysts; 3, simple cysts; 4, conglomerate cysts, polycystic disease or cystic metamorphosis of the kidney; 5, hydatid cysts; 6, paranephric cysts or cysts which are external to the capsule and formed in the circumrenal fatty tissue, but which are intimately adherent to the kidney and sometimes communicate with the renal cavity. The specimen reported in this presentation was apparently one of the fourth group. These are nearly always bilateral and the entire kidney structure is affected, both medullary and cortical portions alike. Because it was unilateral the case reported is rather unusual. Banssillon and Guichard⁴ discussed theories concerning the pathogenesis of polycystic disease of the kidney under the headings of the hematologic theory, the theory of congenital weakness, that of cicatricial sclerosis and that of productive inflammatory hyperplasia. These writers are inclined to the theory of inflammatory origin because of the numerous inflammatory inclusions in the intercystic walls. These lymphoplasmocystic layers, which are frequently intraglomerular and sometimes perivascular, point to an infectious process of perhaps hematogenic origin.

Masmonteil and Schreiber²¹ reported a case of a child who had a bilateral congenital hydronephrosis. The interesting point in this case was the fact that the child survived. At the age of 3 years the first operation was performed. At this time the left kidney was found to be entirely cystic and was removed. Two years later there appeared recurrent attacks of pain and anuria followed by polyuria. The attacks became more severe and more frequent and the patient was admitted

to the hospital after he had had retention for 3 days. At the second operation, the dilated renal pelvis was exposed and opened. It contained a dark, cloudy urine. A Nélaton catheter was inserted and the wound was partially closed. The child was relieved at once but no urine passed into the bladder. It was shown that there was an obstruction at the vesical orifice of the ureter. At a third operation, a transplantation of the right ureter was performed and after 10 days urinary drainage was established through the right ureter. The restoration of function in the sole remaining kidney was a very unusual result for this commonly fatal condition.

Schulz²⁸ stated that Herxheimer noted the presence of hyaline glomeruli in the kidneys of 80% of newborn infants and nurslings examined by him. He ascribed such glomeruli to maldevelopment and regression of completely developed glomeruli. The author, working in Herxheimer's laboratory, made a microscopic study of the kidneys of 52 fetuses and very young infants. His material consisted of 11 fetuses less than 48 cm. long, 15 newborn infants, 8 nurslings up to 1 month of age and 18 nurslings over 1 month. Hyaline glomeruli were seen in 90.3%. The 5 cases in which such glomeruli were not found were fetuses less than 35 cm. long. The most common localization of hyaline glomeruli was in the middle and deep zones of the cortex. As a rule, they were present in otherwise normal kidneys, although they were associated occasionally with focal subacute inflammatory lesions in the kidneys of the older infants. Although focal inflammation may lead at times to hyalinization of isolated glomeruli, the occurrence of the process in the kidneys of fetuses and in kidneys that reveal no degenerative or inflammatory reactions lead the writer to conclude that hyalinization of isolated glomeruli of infants is usually the result of maldevelopment.

For Dietl¹² albuminuria in childhood is either a sign of organic disease or merely a functional disturbance. The underlying organic disease may be external, such as an infection of the efferent urinary pathways, cystitis or pyelocystitis. On the other hand, it may be strictly renal, such as an inflammatory process in the glomerular apparatus which is called a nephritis, or a degenerative process in the tubular apparatus which he termed a nephrosis. Pure forms are rare as there are nephritides with nephrotic features and *vice versa*. Dietl called attention also to functional albuminuria in the child. This is usually called orthostatic albuminuria because it only occurs in the erect posture. One theory of the cause of this phenomenon is that a change from the horizontal to the erect posture causes in these vasolabile individuals a whole syndrome of vasomotor weakness, or a circulatory reaction, of which the albuminuria is only a rather unimportant partial symptom. The direct cause of it may be a relative ischemia of the kidneys, which goes with the rest of the changes such as accumulation of the blood in the abdomen, relative ischemia of the heart and brain and the like.

Nowak²⁴ examined 4500 boys between the ages of 14 and 17. Orthostatic albuminuria with lordosis was present in 248 (5.5%). Orthostatic albuminuria without lordosis was present in 276 (6.1%). Chronic kidney trouble was present in 36 (0.8%). Classifying the cases with lordosis, he found that there was some relationship between the degree of lordosis and the severity of the symptoms. The absence of lordosis in so many cases led him to seek other causes and he redivided the boys

into another three groups: those with general muscular flaccidity and postural defects, those with special susceptibility to catarrhal infections with adenopathy and large tonsils and a miscellaneous group with neuropathic tendencies, dental caries and chronic disease of the middle ear. In the first group there were 142; in the second, 77; in the third, 29. He concluded that lordosis is probably a definite cause of orthostatic albuminuria, but that the condition can be brought on by many other constitutional abnormalities that lead to changed circulation in the kidneys.

From the standpoint of malignancy, Mixter²³ reported that during 21 years in 22,000 admissions to the surgical wards of the Children's Hospital in Boston there were recorded 41 instances of renal neoplasm. It was found that malignant growths occurred in childhood at any age irrespective of sex. Most of them were seen in the first 5 years of life. Symptoms were usually absent at first in childhood but as the tumor grew the child became irritable and gave evidence of abdominal discomfort, although pain was rare. There was usually secondary anemia. In the terminal stage, there were dilatation of the superficial abdominal veins and rapid wasting. Metastases usually occurred by way of the blood stream and involved the lungs, liver and occasionally the opposite kidney.

Campbell⁹ estimated that about one-half of all children suffer from some urologic disturbance at some time before puberty. Many of these disturbances are minor and very frequently are not recognized. On the other hand, many important conditions are overlooked through failure to make simple routine examination of the urine of all sick children. The most common symptoms met with in children having urologic lesions are pyuria, disturbances of urination and nephritis. Obstruction is found to be the most frequent predisposing cause of infection. Congenital stricture is the most common abnormality of the upper part of the urinary tract, but the obstruction may occur at any point from the preputial orifice to the renal calyx. Aberrant renal vessels are a frequent cause of obstruction and about one-fourth of all kidneys have some anomalous vessels. The embryonal adenomyosarcoma of Wilms is the most common abdominal tumor found in children, but hydronephrosis is the most common palpable renal tumor in children.

Anderson³ called attention to the fact that deposition of calcium in the kidneys occurs frequently in infancy and childhood in association with a variety of conditions. Occasional small deposits seem to have no significance. He reported 20 cases of marked renal calcification. The calcium was most frequently limited to the cortical region and involved tubules. In 4 patients who had received parathyroid extract and calcium salts, the deposits were also found in small blood-vessels. Evidence of renal damage was almost invariably found both clinically and at autopsy. Capon¹⁰ also reported a case showing renal calcification but his case showed a renal rickets. Roentgen examination of the kidneys showed calcareous deposits in the calices of both kidneys, the pelves and both ureters.

In a study of urinary lithiasis in infants and children and in a review of the literature Ercole¹³ found a lower incidence in his series; of 60 cases reported, 8% were in children. There was no predilection of sex.

Most of the calculi were formed of uric acid crystals or urates, calcium oxalate or triple phosphates. Calcium oxalate and ammonia urates formed the nuclei in the majority of the cases. These two substances were four times as frequent as uric acid. The presence of triple phosphates indicated the changes due to infection as a result of the calculi. The majority of the calculi (70 %) were found in the bladder.

Aldrich¹ has advocated a classification of nephritis in seven groups, based on clinical signs rather than on anatomic involvement. The first group was called acute postinfectious hemorrhagic nephritis and was characterized by an antecedent or concomitant acute febrile infection, hematuria and either a benign course or death during the acute illness. Second, chronic non-specific nephritis, was characterized by edema, hematuria, hypertension, increase of non-protein nitrogen in the blood and a chronic course or death. The third group, nephrosis, was characterized by marked edema, absence of hematuria at all times, normal blood pressure, normal blood non-protein nitrogen and marked albuminuria. The fourth group, subacute bacterial endocarditis with nephritis, showed edema, signs of subacute bacterial endocarditis with albumin, casts, red and white blood cells in the urine. The fifth group, syphilis with nephritis, showed the clinical picture of chronic non-specific nephritis, or Group II, plus the evidence of an active syphilis. The sixth group, tuberculosis with nephritis, also gave the clinical picture of Group II plus the evidence of miliary tuberculosis. The seventh group, renal infantilism, also showed the clinical picture of chronic non-specific nephritis but in addition the physical evidence of infantilism.

Bell⁵ suggested that subclinical glomerulitis differed from clinical glomerulonephritis only in intensity. A large number of infectious and toxic processes are concerned in the etiology of the disease. The glomerular capillaries are injured by various toxic substances. Sensitization to bacterial or to other protein may play an important part; but it is not necessary to assume that sensitization is essential in the development of the lesion. From a study of a large series of cases it was concluded that a definite preponderance of endothelial over epithelial cells represented a glomerulitis. The glomerulitis seemed to be due chiefly to endothelial proliferation, but the lodgment of mononuclear leukocytes in the capillaries also played a part of some importance. There was no anatomic base for a diagnosis of focal glomerulonephritis except in instances of transitory glomerular bleeding not associated with symptoms of nephritis, and in cases of bacterial endocarditis.

Snoke³⁰ was convinced that glomerular nephritis in childhood was a much more serious disease than is generally believed. After the initial attack the disease may persist for many years. The existence and persistence of latent glomerular nephritis often escapes detection when quantitative examination of properly concentrated urine is not made. It is to be remembered that glomerular nephritis commonly and nearly always enters a latent stage after the initial stage. It is possible for the initial stage to be overlooked when gross hematuria or fulminating symptoms are absent. Latent glomerular nephritis may terminate in healing or may pass on to the degenerative stage or to the terminal stage. The duration is exceedingly variable, and the later stages may not appear until adult life. The prognosis for the successive stages of

glomerular nephritis, active, latent, degenerative and terminal, are successively worse in the order named and the last named is uniformly fatal. The age of the patient at the onset of the disease did not seem to have any influence on the prognosis. Hypertension and increased amounts of blood urea have similar significance and tended to parallel each other. In the initial stage, there is no relation to prognosis of hypertension and increased blood urea concentration, but when they appeared in the later stages they supplied the first indications that the patients were entering the terminal stage of renal insufficiency. The value for blood urea did not become abnormally high as a general rule until one-half of the renal tissue failed to function.

According to Bierman,⁶ the diagnosis of acute glomerular nephritis is based on the sudden appearance of red blood cells, casts and albumin in the urine accompanied by some edema and rise in blood pressure either during or following some acute infection such as tonsillitis or scarlet fever. In a majority of cases the symptoms gradually subsided, the urine cleared up in the course of a few weeks and the child seemed well in every way. He described the Addis sediment count or concentration method (a 12-hour specimen of urine is rendered acid and concentrated simply by restricting the fluid intake for the day preceding the test; after timed centrifugalization the sediment is transferred to a blood-counting chamber and the computations made on a 12-hour basis). Four stages of glomerular nephritis have been established through the studies of Addis. The initial stage follows an acute infection which may have been definite or so mild as to have escaped notice. In its more severe form it is characterized by gross hematuria imparting a mahogany brown color to the urine, edema, vomiting, headache, some elevation of blood pressure and occasional severe prostration and convulsions. This initial stage may go on to healing or progress to more advanced stages. The second or latent stage may be asymptomatic but may be diagnosed by the continued excretion of red blood cells, casts and albumin which may be so slight as to escape notice. This stage may last a few weeks or several years. The third or degenerative stage is characterized by marked albuminuria with large numbers of casts, epithelial cells and leukocytes, together with a small but noticeable excess of red blood cells. Sometimes a decrease of serum albumin, increased plasma lipoids and general edema may occur. Without the Addis test this stage may be confused with a nephrosis. The fourth or terminal stage is characterized by the appearance of headache, vomiting, retinal changes, hypertension and azotemia together with increased amounts of albumin, blood, epithelial cells, and casts. This stage may last only a few days or many months.

Glanzman^{17a} stated that glomerulonephritis is by far the most common form of kidney disease in childhood. He pointed out that it is typified by the picture seen in scarlatina nephritis. Puffiness of the eyelids, especially in the morning, or hematuria or both are early symptoms. There is an increase in body weight due to the latent dropsy. The kidney symptoms are often preceded by a striking yellowish pallor. Oliguria, moderate albuminuria, granular casts, hypertonia and increased residual nitrogen in the blood are characteristic. Even more common than scarlatinal nephritis is a form seen with impetigo or other infectious skin diseases.

Rubin and Rapoport^{25a} found three major complications of acute hemorrhagic nephritis in children: renal failure, hypertensive encephalopathy and eclamptic uremia and cardiac failure. These complications may occur alone or together or may follow each other in the same patient. In the renal failure there were encountered anuria; edema; retention of nitrogenous waste products, urea and creatinine; retention of acid waste products as manifested by the elevated phosphate in the blood and an acidosis as evidenced by low blood carbon dioxide combining power; progressive intoxication as the anuria continued and usually only slight elevation of blood pressure. With the hypertensive encephalopathy there were convulsions, coma and aphasia. The cardiac complications were by far the commonest and most serious complications of the disease. These were hypertension, varying degrees of cardiac involvement, simple dilatation without myocardial failure, cardiac dilatation with myocardial failure, generalized edema and a high blood urea concentration.

Rubin and Rapoport^{25b} studied 55 cases of acute hemorrhagic nephritis in children. Severe myocardial damage was encountered in 14 of the patients and 12 had signs of frank cardiac decompensation. Hypertensive encephalopathy was found in 5 and uremia in 2. The only 2 deaths in the whole group were due to acute cardiac failure. The clinical evidences of cardiac involvement included dyspnea, tachypnea and cough, cardiac enlargement, muffled heart tones, rapid heart rate, murmurs which were usually mitral systolic, gallop rhythm, enlargement and tenderness of the liver, engorgement of the venous system, pulmonary edema, peripheral edema and electrocardiographic changes. They emphasized the importance of hypertension as a cause of cardiac decompensation as they found hypertension in all cases in which there was cardiac involvement.

Discussing chronic nephritis in childhood, Geldrich¹⁶ advocated the classification of the hematogenic renal diseases of Volhard and Fahr. In the group of monosymptomatic forms there is first nephrosis, the cardinal symptom of which is edema. The next heading is sclerosis, the cardinal symptom of which is hypertonia. The third heading is focal nephritis, the cardinal symptom of which is hematuria. Under the group of polysymptomatic forms there is the heading of diffuse glomerulonephritis, in which are united all the cardinal symptoms of the monosymptomatic group. These are further subdivided into an acute type which is curable and a chronic type which is incurable and progressive.

Bruce⁸ gave a simple but adequate classification of nephritis in childhood as acute nephritis, chronic nephritis and nephrosis. Lyttle²⁰ stated that the two common kidney conditions found in children are acute glomerular nephritis or hemorrhagic Bright's disease and nephrosis or degenerative Bright's disease. Of the latter, he listed as typical clinical findings an insidious onset without preceding infection, edema, albuminuria, oliguria with high specific gravity, low serum protein, high blood cholesterol, low basal metabolic rate, a chronic course and pathologically tubular degeneration.

Waring²³ stated that the symptoms of nephrosis are quite classical and well recognized. Edema is usually the first symptom and is insidious in its approach. The urinary changes include albuminuria which

is marked and constant, and casts at times and at other times none. There is a noticeable absence of the cellular elements, particularly the red cells. Oliguria is marked. Doubly refractile lipid bodies are sometimes found. The blood changes include lipoidemia with a marked increase of blood lipoids, especially cholesterol. There is usually a reversal of the usual albumin-globulin ratio of 2 to 1 with general low protein content. The anemia may be marked. The basal metabolism rate is often low although there is apparently no change in the secretory activity of the thyroid gland. Fatigability is a natural and constantly present symptom. As opposed to the changes of glomerular nephritis, there is usually a normal non-protein nitrogen, normal blood pressure and absence of hematuria. The functional kidney test may be normal and there is an absence of uremic symptoms.

Westcott and Dennett³⁴ described nephrosis as a metabolic disease accompanied by changes in the blood lipoids and proteins, and manifested pathologically by degenerative processes. The cause of this condition is not known. Edema is an outstanding feature, but it is not directly of kidney or circulatory origin and is not entirely related in cause or effect to the blood proteins. The authors believed that it was of metabolic origin and that it followed more or less directly the blood lipoids and their metabolism with the resulting change in tissue osmosis due to depleted proteins and increased cholesterol. There is usually an anemia accompanying this condition. This is out of proportion to the loss of kidney function. They felt that the prognosis of primary nephrosis was unfavorable and the same was found to be true of the secondary types that result in chronic nephrosis. The lesion is essentially a lipoidal degeneration with a superimposed infectious element.

Schwarz and Kohn²⁹ found that there was no constant relationship between the height of the blood-cholesterol level and the basal metabolic rate. There was also no constant relationship between the total serum proteins and the patient's weight. In the same way, the body weight, which was a criterion of the extent of the edema, showed no constant relationship with the blood-cholesterol content. When the serum-protein value was low the cholesterol content was usually high, but even this was not constant. This indicated that an increased blood-cholesterol content did not always take the place of the proteins lost from the blood. In cases with a low serum-protein value it was usually the albumin that was excreted. However, in several cases in which the serum-protein value was low, the authors did not always find the expected reversal of the albumin-globulin ratio. They did not find a constant relationship between the intensity of the edema and the amount of protein lost in the urine. The blood-cholesterol content often remained high after all signs of edema had disappeared.

According to Glanzman,^{17b} nephrosis in childhood begins gradually with fatigue, loss of appetite, pallor and slight edema of the eyelids at first. In contrast to acute glomerulonephritis there is rapid development of severe general edema with ascites, hydrothorax and even hydropericardium. The quantity of the urine is slight, with a high specific gravity. The urine contains a great deal of albumin, casts of all kinds, especially lipoid casts and double-refracting lipoid bodies, but no red blood cells. The blood serum and the exudates are clouded because

of the large lipid content. The blood pressure is not increased and real uremia never develops. The child's body seems filled almost to the bursting point with water and then suddenly there is a loss of the edema. This may remain cleared until a new attack develops following a slight infection such as a coryza or bronchitis. The patient is usually a chronic invalid and may die of some intercurrent infection such as pneumococcic peritonitis.

Farr^{14a} made nitrogen balance studies on a group of children with the nephrotic syndrome. He used diets which varied in protein content from 0.5 to 4 gm. per kilo of ideal body weight. The maximum nitrogen retention occurred in 4 patients when the dietary protein intake was about 3.2 gm. per kilo of ideal body weight, and in the fifth patient when the intake was 3.6 gm. per kilo of ideal body weight. Feeding more protein resulted in actually less retention. The protein intakes producing maximal assimilation in these nephrotic children were similar to those found by other observers to be optimal for growth and general condition in normal children. He did not find that in the nephrotic syndrome the loss of protein in the urine was accompanied by compensatory increases in ability to assimilate food protein. It was found that there was no support for the supposition that, in patients with albuminuria, the optimal protein intake could be calculated by adding to the ordinary maintenance diet an amount of protein equal to or proportional to the protein loss in the urine. This group failed to assimilate protein fed above 3.3 gm. per kilo, and this emphasized the point that the physiologically optimum intake of a given food is not necessarily the greatest amount that can be handled by the alimentary tract. Still less was there justification for forcing high protein diets such as those to which are added casein or lactalbumin as this might cause gastro-intestinal rebellion.

Blackman⁷ studied the etiology, pathogenesis and nature of lipid nephrosis. He concluded that there was no evidence that lipid nephrosis is a metabolic disease. He presented clinical and pathologic data which indicated an etiologic relation between chronic pneumococcic infection and the pathogenesis of some examples of lipid nephrosis. He believed that it was a particular form of diffuse nephritis and that microscopic hematuria and slight elevation of the blood pressure may occur at times. From his data he believed that the edema of nephrosis cannot be explained by mechanical factors alone, and that there is good evidence that widespread capillary damage is one important factor in the pathogenesis of edema of nephrosis.

Mitchell *et al.*²² made metabolic studies on 5 nephrotic children. They found that the effects of diuretics and dietary treatment varied greatly in producing temporary changes. No prolonged general improvement, including the disappearance of edema, was accomplished with any procedure. The protein content, including the albumin and globulin of the serum, its non-protein nitrogen content and cholesterol content of the blood were determined from time to time. These values were found to be those characteristic of the nephrotic syndrome. These included a low total protein content, a reversal of the ratio of albumin to globulin, a normal value for serum non-protein nitrogen and a high content of blood cholesterol. The concentration of hemoglobin and the cell counts showed no definite changes. The values for

basal metabolism of all the patients were within normal limits according to the standard of Benedict and Talbot, and with one exception to the standard of Harris and Benedict. According to Dreyer's standard the heat production of all patients except one was low. From the determination of caloric intake and caloric loss, calculations were made for the percentage absorption of energy and the expenditure of energy for growth, digestion and activity. These values agreed with data obtained from normal children and indicated that the energy exchange of a nephrotic patient is normal.

Farr^{14b} stated that in the majority of instances the basal metabolic rate of children with nephrosis was reported as low. All of the patients were in hospital when these observations were made and all manifested well-defined evidences of the nephrotic syndrome, as manifested by edema, lowered level of albumin in the plasma with reversal of the albumin-globulin ratio, absence of hypertension, lack of retention of nitrogen and definite albuminuria without hematuria. Throughout the periods of observation they were all given comparable weighed diets and there were no known complicating factors. This study comprised 34 tests made on 8 patients. There was no significant deviation from the expected metabolic rates with one exception. It was interesting to note that in no instance was a consistently low basal metabolic rate obtained, but it seemed to be increased in 1 patient. This patient seemed to have a real nephrosis. In another study this same patient did not show increased tolerance to thyroid, nor was he benefited by its administration.

Schiff²⁶ stressed the importance of the differential diagnosis between nephritis and nephrosis. He said that if a nephrosis is diagnosed and treated for months as a severe nephritis the treatment probably does more harm than the disease itself. The diagnosis of nephrosis may be made on the presence of edema, with or without ascites, developing suddenly without any premonitory signs, a urine with high specific gravity, an abundance of albumen; no hypertonia. In addition, the eye-ground examination showed a normal fundus, there were a cholesterinemia, a lipidemia, substances with double refraction in the urine sediment and pronounced acceleration of the sedimentation rate of the erythrocytes. It was more difficult to determine whether the case was one of genuine nephrosis or a case of subchronic glomerulonephritis in the stage of nephrosis. Under such circumstances the history is important as the presence of a previous acute nephritis indicated the diagnosis of glomerulonephritis.

In a study of 45 children with the nephrotic syndrome, Tappan³² attempted to determine whether prognostic criteria could be found which might serve to differentiate cases within the group as well as the general prognosis of the nephrotic syndrome in children. It was found that the outlook was grave for these patients. The mortality rate was 51.1% and the recovery rate only 17.7%. The occurrence of hematuria, whether gross or of lesser grades, associated later in the disease with rising blood pressure, increasing retention of nitrogen and diminishing renal function was one adverse picture, and the occurrence of a pneumococcic peritonitis was another development of grave import. It was found that the outlook was grave for patients with the nephrotic syndrome. When hematuria develops the prognosis becomes hopeless

and the occurrence of a pneumococcic peritonitis markedly decreased the chances of recovery in the cases without hematuria.

Discussing the treatment of nephrosis, Schultz and Collier²⁷ pointed out that besides its chronicity one of the most disconcerting characteristics is the tendency to alternate remission and severe exacerbation and the reappearance of the condition after long periods of apparent cure. Although considerable progress has been made in the treatment of the condition, no form of therapy is really consistently successful or gives assured relief for the more troublesome symptoms. Among these are the excessive and sometimes tremendous losses of protein in the urine and the development of anasarca and ascites to a degree seldom met with in pediatrics. The albuminuria cannot be prevented, but can be overtreated to the great harm of the patient when excessive limitation of the protein intake is ordered. It has been found that considerable changes in the protein content of the diet have little or no effect on the daily proteinuria. The edema is a great problem in the care of the nephrotic child. Rest in bed is always absolutely essential. Hydrotherapy only helps to a slight degree. Restriction of salt and restriction of fluid intake is of the greatest importance and is usually most helpful. Among other procedures there are recommended thorough removal of focal infections, especially of the upper respiratory tract. These observers had favorable experience in the few cases in which they could employ it with high administration of alkalis as recommended by Osman.

Aldrich, Stokes, Killingsworth and McGuinness² treated 9 patients suffering from typical lipid nephrosis with edema by administering concentrated human blood serum. In 6 cases the lyophile serum produced complete and immediate diuresis. In 1 patient there was delayed and incomplete diuresis, while in 2 cases no beneficial results were noted. Four patients not only lost their edema but had normal urine within a few weeks of treatment and had remained clinically well up to the time of the report. They believed that the injection of human lyophile serum produced some diuretic effect, but they were not certain that the effects produced were the result of a strictly quantitative osmotic action of the serum. If such were the case, they would hardly expect the diuretic effect to go on for many days until the edema was completely eliminated without replenishment with more concentrated serum protein. They suggested that, in addition to its osmotic action, the serum supplies some substance or substances that set off the patient's own mechanism of diuresis.

A number of references concerning renal dwarfism are met in the literature. Debré, Marie and Jammet¹¹ called attention to a rather curious disease entity which has been described under such terms as renal dwarfism, renal infantilism, renal rickets or chronic atrophic nephritis of childhood with arrest of growth and osseous deformities. They discussed those aspects of the chronic atrophic nephritis of childhood which appeared to them to be especially noteworthy. They called attention to the dwarfism, the normal intelligence and the fact that the secondary sexual characteristics fail to develop at the time of puberty. They also reported their observations on the phosphorus and calcium metabolism. In renal rickets there is a hyperphosphatemia and a hypocalcemia, but tetany rarely occurs. This has been ascribed

to the acidosis in renal rickets, which prevents tetany by transforming the largest portion of the calcium into the ionized form. The first manifestations of this renal trouble is manifested usually about the sixth to tenth year. Polydipsia and polyuria are usually present much earlier. The pallor and jaundiced color of the children are outstanding.

Other forms of kidney disturbances are met with in children. Pyelitis is of very frequent occurrence. Enuresis is another frequent abnormality of this system. Although it is not always due to a disturbance of the kidney itself, it is a very frequent and difficult problem in childhood.

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PHYSIOLOGY.

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 15, 1939

A Flicker Spectrophotometer. R. H. PECKHAM and R. H. HAMILTON (Departments of Opththalmology and Biochemistry, Temple University). Parallel light from a diffuse source is passed through colorimeter cups and plungers and then through sector diaphragms by means of which known fractions of the light can be occluded. The parallel light is brought to a focus upon the sharp edge of a revolvable semicircular front surface mirror, the beams from the two sides being brought into apposition by means of three other front surface mirrors. An eyepiece

focuses upon the mirror edge and projects an image of the diaphragm smaller than the pupil into the plane of the pupil. The observer sees a circular field divided by a diametral line, as in the ordinary colorimeter, and matches of the two halves can be made either by adjustment of the depth of solution or by adjustment of the sector diaphragms.

With a second eyepiece the mirror edge can be focused upon the slit of a monochromator, so that comparisons can be made with monochromatic light. If the sector diaphragms are used to measure the light absorbed by a colored solution at various wave lengths, absorption curves can be plotted.

When the revolvable mirror is driven with a motor to throw light from each side alternately into the pupil, the "flicker phenomenon" produced allows accurate photometric measurements to be made by elimination of the flicker.

Growth and Differentiation of Connective Tissue as Observed Microscopically in the Living Rabbit. MARY L. STEARNS (Fellow, Department of Anatomy, University of Pennsylvania). The daily progress of connective tissue regeneration was followed microscopically in the living rabbit in a series of transparent chambers inserted in the ear. The actual differentiation of connective tissue fibrils was observed.

The new growth began within a week after operation, when fibroblasts invaded the table migrating inward at an average rate of 0.19 mm. a day. Fibrils appeared 4 or 5 days later at the edge of the table. They were extended from the periphery to the center of the table at a rate of approximately 0.27 mm. a day, and covered the entire table, 6 mm. in diameter, 3 weeks after operation.

The observations indicate that the presence of fibroblasts is essential to the development of connective tissue fibers which occurs in the rabbit's ear chamber. Furthermore, fibroblasts participated actively in the formation of the first network of fibrils. Small masses of the protoplasm of the fibroblasts were seen to project from or to become detached from the surface of the fibroblasts. These cytoplasmic masses became centers for very active fibril formation, and rapidly diminished in size as the fibrils formed.

There was no indication that fibers were formed by a direct transformation of the fibrin net that follows insertion of the window. In fact the presence or absence of fibrin was immaterial to the process. No evidence was found to indicate that fibers were formed as continuations of preëxisting fibers, or through the activity of any cell but the fibroblast.

Tension influenced the rate, amount, and direction of fibrous development.

The Action of Urea Upon Hemoglobin. A Spectrophotometric Study of the Process of a Protein Denaturation. DAVID L. DRABKIN (Laboratory of Physiological Chemistry, University of Pennsylvania). With the chromoprotein hemoglobin, visual spectrophotometry was employed in following quantitatively the progress of protein denaturation by various means.

Essentially analogous spectroscopic changes were found to occur when

hemoglobin was treated with alkali, urea and acetamide in high molar concentrations (4 to 6 M), or HCl (0.1 M). In the case of the latter reagent, the familiar acid hematin is produced. The reaction takes time. When, during the course of the reaction, enough alkali was added to just dissolve the material precipitated at the iso-electric point as the acidified solution was neutralized, the presence of typical globinoferro-porphyrin (reduced, denatured globin hemochromogen) was disclosed upon addition of $\text{Na}_2\text{S}_2\text{O}_4$.

The primary reaction during denaturation may be typified by the following:

$\text{Ferrohemoglobin (HbO}_2\text{)} + \text{NaOH} \rightarrow \text{Globinoferriporphyrin (oxidized, denatured globin hemochromogen).}$

With a final concentration of hemoglobin of 0.1 mM per liter (1 mole equivalent to 1 mole of iron porphyrin) and a concentration of alkali equal to 0.008 M, the time required for one-half completion of the above reaction was 13 hours for horse HbO_2 , contained in a closed 1 cm. cuvette at 20°C . Under similar conditions, the reaction was somewhat more rapid with dog HbO_2 . The alkali employed was a mixture of 0.005 M NaOH and 0.003 M NH_4OH . The latter was included to more than compensate for slight ammonia production which occurred in experiments in which both alkali and urea were used.

The rate of denaturation of HbO_2 in the presence of 6 M urea alone, at 20°C ., was of the same order of magnitude as with the above 0.008 M concentration of alkali. The rate of reaction was decreased at lower concentrations of urea, and was appreciably increased at a temperature of 38°C . In the presence of 6 M urea and 0.005 M NaOH, both horse and dog HbO_2 were denatured approximately 60 times as rapidly (13 minutes for one-half completion of the hemoglobin to hemochromogen reaction) as with 0.008 M concentration of alkali alone. This observation is of great interest from the standpoint of the effect of urea upon the molecular structure of hemoglobin.

Ketone Formation and Utilization in Normal and Diabetic Cats. W. C. STADIE, F. D. W. LUKENS, and J. A. ZAPP, JR. (Department of Research Medicine and the Cox Institute of the University of Pennsylvania). Ketone body formation and utilization respectively were studied in normal 3 to 4 day fasted and diabetic cats. Liver slices and muscle mince-meat were equilibrated for 2 hours at 38° in Warburg vessels, and the contents were then analyzed for beta-oxybutyric and aceto-acetic acid. The mean ketone formation of diabetic liver slices was found to be 1052 ± 220 micro-moles/kilo of cat/hour, ($\mu\text{M/Kg/hr}$), while the mean for normal fasted cats was $230 \pm 45 \mu\text{M/Kg/hr}$.

Utilization of ketone bodies by the intact cat was calculated from the liver production minus the urinary excretion during the hour immediately before death. The mean value in 6 diabetic cats was found to be $970 \pm 215 \mu\text{M/Kg/hr}$. Utilization of ketone bodies by muscle was demonstrated more directly in two ways: (1) A weighed liver slice and weighed portion of muscle mince-meat from the same diabetic cat were equilibrated in a Warburg vessel for 2 hours at 38° . On the assumption that the liver slice produced ketones at the same rate as parallel slices in the absence of muscle, it was found that the diabetic

cat utilized ketones at the rate of $2070 \pm 433 \mu\text{M/Kg/hr}$. The oxygen uptake of the liver and muscle together agreed with the sum of the O_2 uptakes observed for each separately. (2) Sodium aceto-acetate was added to muscle mince-meat and the utilization determined directly. The mean utilization of ketones by normal fasted and diabetic cats was found by this method to be $550 \pm 300 \mu\text{M/Kg/hr}$ (6 cats).

Finally, the ratio of oxygen uptake to ketone formation in the liver slices of diabetic cats was $2.26 \pm 0.50 : 1$ and the corresponding R. Q. was 0.39 ± 0.06 . These observations are not in accord with the hypothesis that one molecule of ketone is derived from one molecule of fatty acid, but are consistent with the hypothesis that each molecule of the higher fatty acids yields four molecules of ketone.

Anoxia of the Central Nervous System Produced by Temporary Complete Arrest of the Circulation.* LAURENCE M. WEINBERGER, and JOHN H. GIBBON, JR. (Harrison Department of Surgical Research, University of Pennsylvania). Previous methods used to establish the time that the brain can withstand the effects of circulatory arrest have yielded varying results. The pathologic alterations following upon a single period of circulatory arrest sufficient to cause permanent neurologic signs but not enough to cause death have not been precisely determined. In an effort to reinvestigate this subject a new technique was devised.

The experiments were performed on cats. At a preliminary operation, the left fourth and fifth ribs were resected along with the overlying muscles, the lung pushed aside and the pericardium sutured all around to the cut edges of the muscles. Six weeks later the animal is anesthetized with ether. A small incision is made over the previous site and the pericardium entered without opening the pleural cavity. A clamp is passed around the pulmonary artery. The animal is allowed to come out of its anesthesia and the clamp is then abruptly closed. Thus the bloodflow to the entire body is arrested. At periods ranging from 2 to 9 minutes, the clamp is released. Artificial respiration with a mechanical respirator is started shortly before the clamp is removed to ensure the saturation of arterial blood with oxygen from the moment the clamp is released. An intra-arterial injection of adrenalin and saline is made and the heart is massaged until the ventricular contractions are strong and regular. The retina is continuously observed from the moment the clamp is released and the end of the period of cerebral anoxia is taken as the moment the bloodflow reappears in the retinal vessels. Artificial respiration is continued until spontaneous breathing is established.

The severity of the postoperative neurologic signs and symptoms, and the extent of the permanent neurologic damage varied directly as the length of circulatory arrest. Animals subjected to 3 minutes, or less, of circulatory arrest recovered completely. Those subjected to periods between 3 minutes and 25 seconds and 5 minutes and 45 seconds showed permanent changes in behavior. Those subjected to circulatory interruption of approximately 6 to $7\frac{1}{2}$ minutes showed varying degrees of

* Aided by a grant from the Josiah Macy, Jr., Foundation, New York.

dementia, blindness, postural and reflex changes all of which remained throughout the period of survival. It was not possible to resuscitate animals for more than a few hours if the circulation was interrupted for more than 8 minutes.

The animals were sacrificed for pathologic study at varying periods up to 6 weeks. The pathologic studies revealed that gross cortical necrosis and tissue disintegration can occur following periods of circulatory arrest no longer than 3 minutes and 25 seconds. From this period up to 7 minutes and 30 seconds, the intensity and extent of the cortical destruction increase. In the animals surviving periods of circulatory arrest in the neighborhood of $7\frac{1}{2}$ minutes the cortex was entirely destroyed, disintegrated and fragmented. The susceptibility of the various regions of the brain to circulatory arrest in descending order are: motor and visual cortex, other portions of the cerebral cortex, Purkinje cells of the cerebellum, lateral geniculate nucleus, hypothalamic nuclei, thalamic nuclei, caudate nucleus, midbrain, pons, medulla and spinal cord.

Production of Ovarian Cysts and Urinary Calculi in Young Rats With Testosterone Propionate.* HARRY SHAY, J. GERSHON-COHEN, SAMUEL S. FELS, and KARL PASCHKIS (Medical Research Laboratory of the Samuel S. Fels Fund). Starting in the first or second day of life, 1 mg. of testosterone propionate (Oretone) was injected subcutaneously 3 times weekly into female rats. A total dosage of 40 to 180 mg. was administered. In addition to changes in the clitoris, vagina, uterus, estrus cycle and endocrine glands which have already been described, we observed the formation of ovarian cysts and urinary calculi.

Of 17 treated females (15 sacrificed and 2 orchidectomized), 12 showed ovarian cysts. These ranged in size from 7 mm. to 50 mm. (longest diameter) and in weight from 948 to 62,600 mg. (weight of both ovaries). The size of the ovaries was independent of the total dosage. The smallest total dosage after which ovarian cysts were found to date was 40 mg. The other 5 animals showed atrophic ovaries. Cystic degeneration or atrophy was found in litter mates receiving the same total dosage of hormone. In 1 animal, one ovary was converted to a large tumor weighing 27,000 mg. while the other ovary was atrophic (weight 10.4 mg.).

Histologically, the tumors were lutein cysts. Occasionally follicular cysts were seen as well in some sections.

In 21 treated females (sacrificed and died spontaneously), 11 showed urinary calculi, marked hypertrophy of the bladder, with varying degrees of distention and distortion of the ureters, dilation of the kidney pelves, and atrophy of the parenchyma.

In 1 animal, the kidney pelvis of one kidney was completely filled by a cast-like stone. In 1 numerous abscesses of the parenchyma were found. Urinary calculi were present in animals with ovarian atrophy. In several animals hypertrophy of the bladder without stones occurred.

* We are indebted to Dr. Max Gilbert, of Schering Corporation, Bloomfield, N. J., for our supply of Testosterone Propionate (Oretone).

Perhaps these were cases in which the stones had been passed. While the injection of testosterone propionate does disorder follicle maturation, it does not even in large doses always cause complete cessation of estrus.

In 6 controls, there were no abnormalities of the genital or urinary tracts. In 15 treated male rats, receiving similar amounts of testosterone propionate and sacrificed to date, no calculi or bladder hypertrophy were seen.

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ORIGINAL ARTICLES.

THE CENTRAL CONNECTIONS OF THE VESTIBULAR
PATHWAYS.

AN EXPERIMENTAL STUDY.

BY WALTER E. DANDY,

AND

PAUL A. KUNKEL,

BALTIMORE, MD.

(From the Johns Hopkins University.)

OUR interest in the unsolved problems of Ménière's disease prompted this experimental investigation on the auditory nerves and cerebellum. The results following section of the vestibular nerves in animals are so different from those obtained in human beings that their transfer to man is impossible. Indeed had the devastating effects of dividing the auditory nerve in dogs and cats antedated the operation on human beings^{1a,b,c,d} the cure of Ménière's disease by this operative attack might well have been delayed.

Apparently there is no difference in the effects produced in dogs and cats except in degree, the cats reacting more severely. The operative attack upon the auditory nerves and the cerebellum was found to be much more difficult in both dogs and cats than upon human beings, largely because of the excessive vascularity about the dural sinuses in the posterior cranial fossa. Bleeding from this source is difficult to avoid, because the dura is so thin and so closely attached to the bone. By "rongeur" the bone very cautiously and in very small amounts at each step, it is possible to separate the dura and stop effectively the bleeding by application of wax. The attack upon either the auditory nerves or the cerebellum is merely a matter of painstaking care. Without a bony defect of

adequate size the soft cerebellum quickly becomes edematous from the effects of trauma and thereby the interpretation of the results may be vitiated by the complications. This warning applies both to section of the auditory nerve and to the removal of the cerebellum. In hemisection the remaining half of the cerebellum may be damaged so severely as to be in large part necrotic. In partial or total section the brain stem may be injured. With either complication the experiment may be so defective that the results will be worthless.

In cutting the auditory nerve the bony defect must be made so far laterally that the cerebellum may be retracted without trauma. Hemisection of the cerebellum is done by splitting the vermis from the tentorium anteriorly to the membranous covering of the apex of the fourth ventricle; this is practically bloodless. The hemisphere then is turned outward and upward until the large peduncle is isolated. This is transected with a scalpel; the cerebellar lobe has only minor attachments along the upper margin of the fourth ventricle. Midsection of the vermis makes either unilateral or total removal of the cerebellum much simpler and practically devoid of trauma to the remaining structures.

Section of the restiform body (middle peduncle) in animals dates back nearly a century. Vulpian⁸ (1866) refers to Magendie's experiments in sectioning the middle peduncle of the cerebellum in cats; rotation of the animal with incredible rapidity followed and to the same side. His results were confirmed by Vulpian, Schiff, Hitzig⁶ and other great physiologists working about the middle of the nineteenth century. The results were the exact equivalent of destruction of the semicircular canals (Flourens' experiments). Ferrier³ (1880) and Ferrier and Turner⁴ (1898) divided the auditory nerve in rabbits and monkeys; their results were similar to those following section of the restiform body. They refer to earlier experiments of this type by Brown-Sequard. In the course of time the rolling movements subsided and the animals walked again, but in a sprawling, unsteady fashion. Ferrier³ comments upon the great mortality attending his attempts to expose the cerebellum in dogs and cats: he "succeeded in comparatively few," but the results were the same as in rabbits.

In recent years, Fulton, Liddell and Rioch⁵ (1930) sectioned the auditory nerve in cats with greater ease and with more assurance that contiguous structures have not been injured. Their results, however, are not different and were identical with labyrinthectomies. They stress the advantage of "dial" (a barbiturate) anesthesia in facilitating the operative procedure, and doubtless the prolonged anesthesia (36 hours or longer) is responsible for the fact that their animals usually survived and after a period of 9 to 13 days walked again, at first in a very poor sprawling fashion, but gradually improving. Owing to the short duration of ether anesthesia all our

animals succumbed within 48 hours, the period in which the severity of the whirling movements is at its maximum. After 36 hours it was found that these movements steadily diminished. This was the experience of Ferrier and Turner and later of Northington and Barrera⁷ (1934) and of Dow² (1938) in monkeys. This also corresponds fairly well with the subjective rotary effects in man following the section of the vestibular nerves. Dow has emphasized the fact that the severity of this disturbance decreases as one ascends the phylogenetic scales. He even found that the effects produced by destruction of the labyrinth in anthropoids (baboons and chimpanzees) were less than in monkeys. Ferrier³ dwells at some length on the shift from the actual rotation of the body in animals, including monkeys, to the purely subjective visual disturbance that attends lesions of the auditory nerve in human beings. At that time the auditory nerve had, of course, not been sectioned in man.

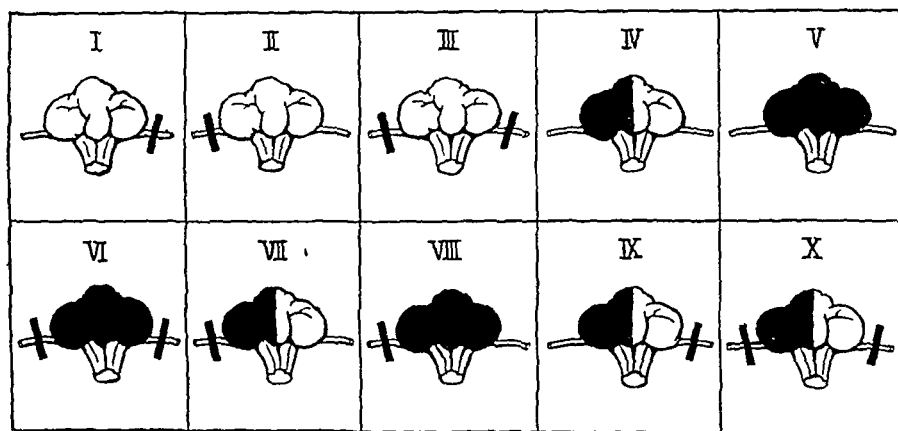


FIG. 1.—Tabulation of experiments.

Our results following section of the auditory nerves in animals are in complete accord with those of all other experimentalists on this line. We are, however, less concerned with these effects than with the central pathways of vestibular function which we believe are concentrated almost entirely in the cerebellum. This view was expressed by Meynert (see Ferrier³), but he apparently also believed that the same was true of the auditory pathways, an utterly untenable concept, according to Ferrier, because his experiments had led him to the conclusion that a center for hearing was located in each temporal lobe—a view, by the way, that modern cerebral excisions have rendered impossible, at least in human beings.

Experiments. In order to avoid repetition only one protocol has been entered for each experiment, although each has been repeated at least once.

I. Adult Cat. Section of right eighth nerve (N VIII) (cerebellar approach); ether, November 15, 1934. The animal stood the operation well; 6 hours later it was awake and nervous. There was facial paralysis on the

right. It lay against the side of the cage on the right side. Placed on the floor it rolled violently to the right, spinning until it finished exhausted against the wall. If placed on the left side, it immediately rolled over and over, but always to the right. It could not stand or walk. Nov. 16: Same reactions. Unable to eat or drink and is fed by tube. Nov. 17: Died. Autopsy showed total section of the right seventh and eighth nerves.

II. *Adult Cat*. Total section of eighth nerve left; ether, November 15, 1934. Exactly the same reactions, except whirling is to the left. Unable to stand or walk.

III. *Adult Cat*. Bilateral section of eighth nerve (cerebellar approach); ether, December 3, 1935. Cat in good condition at end of operation. Six hours later it was awake and lying against the side of the cage. Both sides of the face were paralyzed. It did not respond to noises. Placed on the floor it rolled violently to the right, at other times to the left. It was unable to sit, stand or walk and would not take water or food. Dec. 4: Same reaction as before. Dec. 6: Died. Autopsy showed total section of both seventh and both eighth nerves.

III. (a) *Adult Dog*. Section of nerves VIII, bilateral (cerebellar approach); ether, February 14, 1935. Animal stood operation well. Five hours later marked nystagmus; rolled and spun violently to either side, but not as violently as the cat. Unable to stand, sit or walk. Died following day. Necropsy showed both auditory nerves totally divided.

IV. *Adult Cat*. Removal of left half of cerebellum; ether, January 21, 1935. Six hours later cat awake and quiet. No turning movements and no rolling at any time. Lay on left side; could not sit up or stand.

V. *Adult Cat*. Removal entire cerebellum, January 10, 1935. Cat remained quiet, did not whirl at any time. Could maintain sitting position, but could not stand or walk.

VI. *Adult Cat*. Removal entire cerebellum and section of both nerves VIII; ether, January 14, 1935. Animal stood the operation well. Six hours later it was awake, lying on right side. Gave no evidence of hearing noises. For most part animal was limp and unable to stand; it remained on either side or back when so placed. When picked up by hind quarters with head and front of body hanging, it executed normal movements (coordinated) of forelegs and turned head from side to side. Jan. 15: Same reactions as yesterday. Will not eat or drink. Jan. 17: Died. Autopsy showed complete extirpation of cerebellum and both eighth nerves were totally divided.

VII. *Adult Cat*. Removal *left half* cerebellum and section nerve VIII *left*; ether, January 17, 1935. Six hours later animal in good condition. Placed on floor it turned and rolled violently *to the left*, coming to rest on the left side. Movements began with turning of head *to left* and then body was rapidly turned. Died following day. Remaining half of cerebellum showed no necrosis; eighth nerve had been totally divided.

VIII. *Adult Cat*. Section left nerve VIII and left half of cerebellum removed; ether, January 17, 1935. It has since been whirling *to the left*. Jan. 18: Removed the remaining right half of the cerebellum. Six hours later the cat was awake, quiet and without turning movements. Lay quietly on either side. Picked up by hind quarters, it turned normally either to right or left; moved both forelegs in normal manner. Died the following day. Autopsy showed all cerebellum removed; left auditory nerve was totally divided. Brain stem showed no softening.

IX. *Adult Cat*. Section right nerve VIII and removal of left half of cerebellum; ether, January 30, 1935. Five hours later it was wide awake. Nystagmus present. It lay on the left side in the cage, tried to push itself about but *did not spin*. Regardless of position and movements induced, no

whirling movements could be provoked. When picked up and put on right side it lay quietly. There was a striking contrast to the cats with the cerebellum intact, or with half of cerebellum removed and the ipsilateral nerve VIII sectioned. Movements of all extremities were good. Jan. 31: Same reactions as yesterday. No spinning movements. Feb. 1: Reactions unchanged; it died during the night. Autopsy showed nerve VIII sectioned on right. Right half of cerebellum was in good condition.

X. *Adult Cat*. Section under ether of both nerves VIII and removal left cerebellar lobe, October 18, 1936. Awake 3 hours later, had nystagmus. Rolled violently to the *left* until exhausted. Lay on the right side. Oct. 19: similar violent whirling to *left* only. Died during night. Autopsy showed total division of both eighth nerves and an intact right cerebellar lobe.

TABLE 1.—RESULTS OF EXPERIMENTS.

<i>Operation.</i>	<i>Result.</i>
I. Total section <i>right</i> N VIII	Violent whirling to right; cannot stand or walk.
II. Total section <i>left</i> N VIII	Violent whirling to left; cannot stand or walk.
III. Total section <i>both right and left</i> N's VIII	Violent whirling to both sides; cannot stand or walk.
IV. Removal <i>left</i> half of cerebellum	No whirling; cannot stand or walk.
V. Removal <i>entire</i> cerebellum	No whirling; cannot stand or walk.
VI. Removal <i>entire</i> cerebellum and total section of both N's VIII	No whirling; cannot stand or walk.
VII. Removal <i>left</i> half of cerebellum and total section <i>left</i> N VIII	Violent whirling to <i>left</i> ; cannot stand or walk.
VIII. Removal <i>entire</i> cerebellum and total section <i>left</i> N VIII	No whirling; cannot stand or walk.
IX. Removal <i>left</i> half of cerebellum and total section <i>right</i> N VIII	No whirling.
X. Removal <i>left</i> half of cerebellum and total section <i>both</i> N's VIII	Violent whirling to <i>left</i> .

Summary and Conclusions. A summary of the above experiments in terms of whirling indicates the following:

1. Section of either N VIII results in frequent spells of violent whirling—always rolls to the side of the lesion (Experiments I and II).

2. Section of both N's VIII results in violent whirling—turns to either side (Experiment III).

3. After removal of one-half of the cerebellum there are no rotary movements (Experiment IV).

4. After removal of the entire cerebellum there is no whirling (Experiment V).

5. After section of N VIII and removal of the cerebellar lobe of the same side, violent rotation follows; and the whirling is to the same side (Experiment VII).

6. After section of one N VIII and removal of the opposite cerebellar hemisphere no whirling results (Experiments IX and X).

From these experiments it will be seen that the ability to sit or stand or walk is completely lost immediately after section of either or both auditory nerves, and as far as we can tell the result is, in

this respect, exactly the same as removing either half or all of the cerebellum. The great difference following these two procedures is that after removal of half or all of the cerebellum the animal lies quietly, whereas after section of one or both auditory nerves a terrific whirling of the body results and continues until death results from exhaustion. Fulton, Liddell and Rioch⁵ have shown that after section of one or both auditory nerves under prolonged "dial" anesthetic the severe period may be passed under the anesthetic. When the animal responds after 36 to 48 hours, the rotation is so much less severe that the animal will recover.

The profound effects produced by sectioning one or both auditory nerves are entirely different from those in man.^{1a,b,c,d} The body itself is set in motion in a series of violent whirling movements that are precipitated by any slight movement of the body and always occur to the side of the sectioned nerve, or to either side when both nerves are cut. These violent whirling attacks are immediately abolished when the entire cerebellum is removed.

In man, the body itself does not rotate following section of a vestibular nerve, but the effect is one of rotation of objects in the room, or when the eyes are closed of rotation of the body. In man, therefore, the aberrations of vestibular function are transferred to, and translated by, the visual tracts so that the effect produced is *subjective* and visual; in animals, the untoward effect is somatic and objective. Doubtless the transfer of the vestibular function from the cerebellum in dogs and cats to the visual tracts in human beings is related to a lessened importance of the semicircular canals in man as compared to animals.

In keeping with this change in the functional setup of the vestibular pathways, it is interesting that section of *both* eighth nerves in *man* has little, if any, effect upon the equilibrium of the body, but rather the effect is one of jumbling the appearance of objects when the body is in motion, *i. e.*, the effects are upon ocular coördination. These physiologic effects, therefore, indicate the probability that when the vestibular pathways can be accurately charted, those in dogs and cats will predominantly pass to the cerebellum, whereas those in human beings will pass up the brain stem to the centers controlling the extraocular movements.

The fact that the violent rotary movements of the body are instantly and permanently abolished (in dogs and cats) when both cerebellar lobes are removed doubtless indicates that the central apparatus concerned with equilibrium is very largely, if not entirely concentrated there.

Another striking and perhaps surprising feature of the experiments is the contralateral relationship between the cerebellum and the peripheral vestibular tracts, *i. e.*, bodily rotation after section of an eighth nerve is unaffected by removal of the ipsilateral half

of the cerebellum, but is abolished by removal of the contralateral half. This can only mean that the vestibular pathways decussate like the pyramidal tracts.

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THE VALUE OF COLLOIDAL ALUMINUM HYDROXIDE IN THE TREATMENT OF PEPTIC ULCER.

A REVIEW OF 407 CONSECUTIVE CASES.

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THE treatment of peptic ulcer by the continuous administration of colloidal aluminum hydroxide has now been in use for 3 years. A review of 407 cases in which this method of therapy has been employed furnishes a sound basis for a reëxamination of principles, and for revaluation of results. This treatment represents no radical departure from the methods that have been in use for many years, all of which have been designed to counteract the effects of excessive acid secretion in the stomach. The drip treatment with colloidal aluminum hydroxide merely emphasizes and expands this principle by the use of a more effective neutralizing agent, administered continuously instead of intermittently.

It has been amply proved by clinical and experimental evidence that hydrochloric acid is active, not only in initiating ulcerations of the stomach and duodenum, but also in preventing their healing. The process of repair which consists of deposition of granulation tissue, begins almost coincidentally with formation of an acute peptic ulcer. The corrosive action of hydrochloric acid is the most formidable antagonist to this healing process. If the factors causing the ulcer are dominant over the natural healing process, the lesion progresses steadily, and in time becomes chronic. On the other hand, if the factors producing the ulcer are satisfactorily controlled, then the balance shifts in favor of healing. It follows that treatment, to be satisfactory, should protect the ulcer from acid corrosion continuously, not only during the day, but also throughout the night.

Otherwise, the accumulation of acid at night may destroy some of the granulation tissue formed during the day, and thus delay or prevent healing.

Rationale of Treatment. Although alkaline powders have been, and still are being widely used in the treatment of peptic ulcer, the results obtained with them are not always satisfactory. Their neutralizing effect, which is short-lived, is followed by a marked compensatory stimulation of acid secretion in the stomach. Crohn and Reiss¹ have demonstrated that magnesium oxide, sodium bicarbonate, and so on, are the most powerful known excitants of gastric secretion, aside from histamine. Sodium bicarbonate has the additional disadvantage of liberating carbon dioxide gas, which, if it cannot escape within a few minutes, may accumulate in sufficient quantity to be a potential danger through perforation of an ulcer. Furthermore, the administration of large quantities of alkalis may present potentially the hazard of alkalosis.

It is obvious that the ideal agent for the treatment of peptic ulcer is one that will neutralize hydrochloric acid without producing any general systemic reaction, and without disturbing the secretory or motor function of the gastro-intestinal tract. Colloidal aluminum hydroxide meets these qualifications.

Characteristics of Colloidal Aluminum Hydroxide. Colloidal aluminum hydroxide is a white, gelatinous substance, mildly astringent and non-irritating. It is amphoteric, with a pH of 6.9; hence it may be administered continuously without danger of alkalosis. The preparation contains about 5% of aluminum hydroxide and about 0.6% of sodium chloride; the remainder is water.

Experiments *in vitro* demonstrate that this colloidal product, when undiluted, combines with 12 times its volume of tenth-normal hydrochloric acid within half an hour. It is non-toxic and has no harmful effect, even in large doses. Large quantities of colloidal aluminum hydroxide do not disturb the acid-base balance of the blood, as shown by estimations of the blood chlorides, the carbon dioxide-combining power, and the pH of the blood. There is practically no absorption of aluminum from the gastro-intestinal tract, as shown by Ivy,³ in dogs, and by Einsel, Adams, and Myers,² in man.

Besides its exceptional antacid action, colloidal aluminum hydroxide has the additional advantage that it protects the ulcer by coating it with a jelly-like mass. This adherence to the walls of the stomach can be shown roentgenographically, after the substance is mixed with a small quantity of barium.^{5c} Numerous investigators, including Ivy and his collaborators,³ have reported that in animals receiving preparations of aluminum hydroxide, necropsy frequently shows the mucosa of the stomach and duodenum coated with the material so that it appears as if covered with flour paste.

The astringent action of colloidal aluminum hydroxide is also advantageous in healing the ulcer, and in arresting hemorrhage in bleeding ulcer. Sollmann⁴ has pointed out that "astringents are used therapeutically to reduce inflammation of mucous membranes, promote healing, and to arrest hemorrhage (by coagulating the blood)."

With such a neutralizing agent, which effectively combats acidity, and is absolutely non-toxic, it is safe to make practical application of the principle that the ulcer should be constantly and continuously protected from the corrosive effect of hydrochloric acid. Such treatment abets the natural healing process in its struggle against the antagonistic effect of acidity. To be entirely successful, not more than 1 hour can be allowed to elapse without medication. The treatment must be continued throughout the night, lest the delicate granulation tissue formed during the day be destroyed by accumulation of acid. The granulation bud is extremely friable and easily destroyed, and the ulcer must be protected until sufficient tissue has been deposited to fill in the crater. According to roentgenographic studies, this requires 7 to 10 days.

The same method has been used successfully in the treatment of bleeding ulcers.^{5a} Because of its astringent effect, colloidal aluminum hydroxide hastens the coagulation of blood. The danger in hematemesis, however, arises not so much from a single episode of bleeding, but because of the likelihood of its recurrence. The hemorrhage from a blood-vessel in the stomach usually ceases as suddenly as it begins, when the bleeding point is plugged with fibrin. Destruction of this fibrin clot by acid digestion is the cause of recurrence of the bleeding. Thus the purpose of the continuous administration of colloidal aluminum hydroxide in hematemesis is to promote clot formation and then to protect the delicate fibrin from the action of strong unbuffered gastric juice.

That colloidal aluminum hydroxide does actually prevent digestion of the fibrin clot can be demonstrated experimentally *in vitro*. A clot of blood placed in a test tube filled with freshly aspirated gastric juice, and placed in an incubator at 37° C. shows evidence of digestion within 1 to 2 hours. However, when colloidal aluminum hydroxide is added to the tube containing the gastric juice and a small clot of blood, there is no evidence of digestion after 24 hours. Pepsin is not active in alkaline or neutral solutions.

Technique of Treatment. *Administration by Drip Apparatus.* The technique of administering colloidal aluminum hydroxide by the drip method has been described previously.^{5a, 6a, b} This method of treatment requires hospitalization of the patient. The colloidal aluminum hydroxide, diluted to 25%, is continuously instilled into the stomach through a nasogastric tube at the rate of 15 drops per minute, both day and night, for 10 days. The flow of the drops is regulated and controlled by a special apparatus.

The indwelling nasal catheter was the source of considerable difficulty in some of the early cases. When a No. 12 Levin tube was used, the lumen was so small that it would become occluded by particles of food regurgitating back into the tube, or by coating of the walls by the aluminum hydroxide itself. This, of course, caused cessation of the flow, and necessitated troublesome irrigations of the tube, which corrected the difficulty only temporarily, and therefore had to be repeated frequently. When a large Levin tube was used, many of the patients complained of soreness in the nose and throat, even when the tube was well lubricated with mineral oil, and frequently they would remove the tube themselves when the discomfort became too great.

These difficulties were overcome by using a soft collapsible thin rubber tube about $\frac{1}{4}$ inch in diameter, passed through the nose into the stomach with the aid of a silkworm-gut suture.^{5b} This acts as an obturator and is left in place within the tube to prevent its kinking. This tube has entirely eliminated the difficulties of obstruction of the lumen and discomfort to the patient experienced with the Levin tube. The nasogastric tube is passed only as far as the lower end of the esophagus. This precaution eliminates the rare possibility of any danger of trauma to the lesion.

Oral Administration. In the few instances in which patients objected to or could not tolerate the nasogastric tube, the medication was administered by mouth. One ounce of a 25% suspension of colloidal aluminum hydroxide in water is given every hour during the day until the patient retires, and then he is awakened every 2 hours during the night to receive the same dose. Usually a sedative is administered in the evening, so that the patient falls asleep promptly after being aroused for the medication. With the drip method, of course, the patient rests all night without interruption.

Diet and Supplementary Medication. Along with this treatment in the hospital, the patient receives a bland diet of which small quantities are taken every 2 hours for 12 hours. This consists of milk with one-third cream, cooked cereal (oatmeal, farina and cream of wheat), a soft boiled egg, a slice of toast, butter, cream soups, gelatin, custard, tapioca, and junket. Inasmuch as the astringent action of aluminum hydroxide causes some constipation, mineral oil is given daily, or enemas every other day. A sedative is administered each night to prevent worry about the treatment.

The Treatment of Massive Hemorrhage. The same regimen is employed in cases of hematemesis and melena. As soon as the patient with melena is admitted to the hospital, a soft nasogastric tube is passed through the nose to the cardiac end of the stomach, and the drip treatment is begun. If hematemesis is present, the patient receives colloidal aluminum hydroxide by mouth every hour until vomiting has ceased; then the drip treatment is begun.

These patients receive food every 2 hours, and the diet is the same as that administered to other patients with peptic ulcer. To induce rest, the hypodermic administration of sodium phenobarbital is preferred to that of morphine, because morphine not only interferes with the normal function of the gastro-intestinal tract, but also has the undesirable effect of causing emesis, in some instances.

Small transfusions, usually about 250 cc. of blood, are given when the systolic blood pressure is reduced to less than 90, or when the hemoglobin is below 30%.

Ambulatory Treatment Following Hospital Care. When the course of treatment in the hospital is completed, an ambulatory regimen is continued for 30 days after the patient leaves the hospital, before the healing of the ulcer is considered complete. When the ulcer crater has become filled in

with granulation tissue, which is shown on the roentgenogram by disappearance of the niche, the lesion may still not be healed. It may take more time for the mucosa to grow around the periphery toward the center. Hence this area must be protected against the harmful action of hydrochloric acid, until complete healing, with epithelization, has taken place. Even if the lesion were healed, the regenerated mucous membrane is thin and deformed, and implanted on dense fibrous tissue, with imperfect blood supply, and therefore would require the same protection.

The patients are advised to take 2 teaspoonfuls of aluminum hydroxide in 2 ounces of water every 2 hours until bedtime, and mineral oil at night, along with a convalescent ulcer diet. This diet is limited in quantity, and avoids mechanical, chemical and thermal irritation. In addition to the foods allowed in the hospital, it includes puréed vegetables, stewed fruits, stewed chicken, creamed fresh fish, cottage or cream cheese, rice and macaroni.

Even when the ulcer is completely healed, the underlying diathesis which produced it in the first place still remains, and consequently it is likely to recur. A patient with peptic ulcer should be taught to understand, and to accept the fact that, since the disease is caused by some fundamental physiologic disturbance as yet not well understood, the physician cannot promise permanent cure of the disability. The best that can be offered is to heal the existing ulcer, and to try to prevent recurrence by diet and medication.

Results of Treatment.—In a period of 3 years from September, 1935, to October, 1938, 407 patients with peptic ulcer were treated with colloidal aluminum hydroxide on the medical service at St. Luke's Hospital. In this group, there were 322 men and 85 women. There were only 8 negroes in the group; 399 were white persons.

Approximately 25% of these patients (101) were suffering from acute massive hemorrhage at the time of admission. In 8 patients with hematemesis, the situation of the ulcer could not be determined. There were 285 cases of duodenal ulcer and 83 of gastric ulcer. Twenty-two patients had ulcers in both the stomach and duodenum, and 9 had marginal ulcers (6 of these followed gastro-enterostomy, and 3 followed gastric resection).

The continuous drip method was used for 270 patients, while 86, who were unable to tolerate the nasogastric tube, received the medication orally. Fifty-one patients received colloidal aluminum hydroxide by both the continuous drip method, and orally. In these instances, the nasogastric tube could not be tolerated for the entire period of treatment, and the remainder of the course was given by mouth.

The most striking features of the treatment of peptic ulcer by the continuous administration of colloidal aluminum hydroxide are: 1, the prompt relief of pain, 2, the rapid healing of the ulcer, 3, the healing of refractory ulcers, and 4, the excellent results in cases of massive hemorrhage.

Prompt Relief of Pain. Patients who have had severe pain, and have obtained only temporary relief by diet and alkalis, have

noticed a complete disappearance of pain during the first 24 hours of treatment, and some immediately after it was started.

Rapid Healing of the Ulcer. Roentgenographic studies showed disappearance of the niche in the majority of cases of gastric ulcer at the end of 10 days; in some, as early as 7 days. A longer time, usually about 14 days, was required for filling in the crater of large ulcers. It is much more difficult to demonstrate evidence of healing in cases of duodenal ulcer because the niche so often is not visible roentgenographically in this type. Hence it is necessary to judge the results of treatment of duodenal ulcers on the basis of symptoms and follow-up examinations.

Gastric ulcers frequently heal without a trace, and only occasionally produce an hour-glass deformity. Duodenal ulcers leave a scar deforming the duodenum. The typical niche produced by an ulcer is difficult to demonstrate on a roentgenogram of the duodenum. Even if the niche is found before treatment, its absence after treatment may not mean that the ulcer has disappeared, but merely that the second roentgenogram does not show it. To make the interpretation still more difficult, a healed ulcer in the duodenum may still produce a niche. In 1 case in this series, a large duodenal niche remained after two courses of treatment with aluminum hydroxide, and the patient was sent to surgery for a gastric resection. Exploration revealed that the ulcer was healed, and entirely covered with newly formed mucosa. In another instance, the patient was operated upon elsewhere for the same reason. The attending surgeon reported that the ulcer was healed. These are the only cases, according to the records, in which operation has been performed following the treatment with colloidal aluminum hydroxide.

Healing of Refractory Ulcer. Many of the patients in this group had tried other forms of treatment without experiencing any improvement, and yet have responded rapidly to the drip treatment. Apparently, in the cases of so-called refractory ulcer, the previous failure to heal was due to the accumulation at night of acid which destroyed some of the newly formed granulation tissue. When the medication was applied continuously, both night and day, these same ulcers healed very rapidly.

One patient with a duodenal ulcer had been in bed for 6 weeks on a Sippy diet, plus alkalis, but had received no treatment during the night; he had displayed no improvement at the end of that period. A gastric resection had been advised by his physician, but he decided to try the continuous drip treatment with colloidal aluminum hydroxide instead. After 10 days of treatment, he was free from symptoms and the duodenal cap showed less deformity on the roentgenogram. Other patients have also been spared from operation by this treatment.

In another patient who had had a gastric resection, a large ulcer crater developed at the margin. He was put to bed for 4 weeks on a

Sippy diet, with alkalis; at the end of that period the crater was still present. He then took the continuous drip treatment, and at the end of 10 days, several roentgenograms were made, and they showed a complete disappearance of the ulcer crater.

In 4 cases in which the usual clinical response was lacking, and in which the roentgenographic appearance of large ulcer craters was not altered by the drip treatment, the patients were operated upon, and were found to have malignant lesions. These cases are not included in the present series, since the treatment functioned merely as a therapeutic test for malignancy.

Massive Hemorrhage. From September, 1935, to October, 1938, 101 patients with hematemesis or melena have been treated with colloidal aluminum hydroxide. In this series, there have been but 3 deaths. It is interesting to contrast this mortality rate of 3% with that observed at the same hospital in the 5-year period preceding the inauguration of this form of medical treatment. During that time, there were 38 cases of massive hemorrhage from the gastrointestinal tract, with 11 (29%) deaths.

This group includes only those patients who were admitted as emergency cases for the treatment of massive hemorrhage as the leading, often the only symptom. They were vomiting bright red or dark blood, or had bloody or tarry stools, along with secondary anemia sufficient to produce weakness, pallor, dyspnea or rapid pulse. Patients with blood-streaked or occasional "coffee-grounds" vomitus, occult blood in the stool, or rare tarry stools were not included in this group.

Fifty-six patients had hematemesis, 45 had melena. Sixty-seven had duodenal ulcer; 19 had gastric ulcer; 4 had both types. There were 3 with marginal ulcers (2 following gastro-enterostomy, and 1 following gastric resection). In 19 cases, there was no history of ulcer. In 8, the situation of the lesion could not be found.

The drip treatment was given in 57 cases; 19 patients received the medication orally, and in 14, colloidal aluminum hydroxide was given by both methods.

The 3 patients who died were all white men, aged 45, 51, and 56 years, respectively. The first patient had had a duodenal ulcer for 7 years, and had been vomiting blood for 2 weeks before admission. The drip treatment was administered for 12 days, during which time he had two transfusions. Death occurred following a severe hemorrhage on the twelfth day. Necropsy revealed a chronic duodenal ulcer, 1 cm. in diameter, with a large artery (gastro-duodenal artery) protruding from its base.

The second patient, aged 51 years, gave no history of an ulcer but had been vomiting considerable blood for 2 days before admission. He received colloidal aluminum hydroxide orally for 5 days, during which time he had two transfusions. This patient died on the sixth day, and autopsy revealed a superficial ulcer on the posterior

wall of the stomach, about 1.5 cm. in diameter. Projecting from one end was a large vessel (a large branch of the left gastric artery), about four-fifths of which had undergone necrosis. There was also evidence of generalized arteriosclerosis.

The last patient, aged 56 years, had complained of epigastric distress for about 3 months, and had severe hematemesis at the time of admission. He received colloidal aluminum hydroxide orally for 3 days and two transfusions. He died on the fourth day. It had been impossible to obtain a roentgenogram of this patient's stomach, and permission for an autopsy was not obtained.

It is interesting to note that from September, 1935, to November, 1937, 54 consecutive cases of massive hemorrhage were treated by this method, without a single death. The 3 deaths occurred within a period of 48 days, the first, November 8, 1937, the second, December 6, 1937, and the third, December 26, 1937. Since then, 44 additional cases have been treated, without a death.

A hemorrhage in a person more than 45 years of age may be an indication for surgery, especially when the vessels are sclerotic; on the other hand, there is a fair chance that the patient may never have another episode of bleeding. A single hemorrhage in a person less than 45 years of age is definitely not an indication for operation, but repeated hemorrhage may be.

Surgical intervention in gastric hemorrhage entails great risks. If the bleeding is caused by an acute peptic ulcer, operation is likely to be futile, because there is no external indication of the presence of an ulcer, and the stomach must be opened to deal with the bleeding point. The search for this is so difficult that the ulcer often is not found. In such instances, the shock of the operation, in addition to the prolonged hemorrhage, is almost certain to result in the death of the patient. On the other hand, a chronic ulcer is easily found. However, even in the presence of a known chronic ulcer, operation is inadvisable, because the chronic ulcer may not be the source of the hemorrhage. It is impossible to exclude in such cases a complicating acute ulcer which would probably never be found at operation. Exsanguinated patients, even when they receive blood transfusions, are poor surgical risks.

Recurrences. It is impossible to estimate accurately the number of recurrences following any type of treatment for peptic ulcer. Patients who suffer from this disease characteristically are nervous and high strung. Consequently they are impatient and restless and in some cases not so coöperative with their physician as they should be. They resent the chronicity of their illness and the prolonged treatment which it requires and are always seeking the physician who will promise them a quick and permanent cure.

The occupations and environments of many of these patients subject them to great nervous strain which undoubtedly aggravates the severity of their symptoms. Consequently the physician often

advises the patient to change his environment and method of living if he wishes to obtain relief from peptic ulcer. This advice is excellent in theory but, in my experience, can seldom be applied in practice.

Knowing that, for economic reasons, the majority of patients with peptic ulcer are going to continue to be subjected to work and worry that induce nervous strain, and that there is little or nothing that they can or will do about it, it is necessary to offer them medication which will counteract the consequences of the tension of modern living.

Apparently all peptic ulcers begin as acute lesions and possess originally a strong tendency to heal. Frequently, however, they are prevented from doing so by certain peculiar influences to which they are subjected. Hyperacidity can convert an acute ulcer into one of the chronic type, as has been shown experimentally. It follows that, if the acidity of the stomach could be controlled absolutely, and for an indefinite period of time, the recurrence of a chronic peptic ulcer should be prevented.

Since peptic ulcer is, in most cases, a chronic disease, it requires prolonged treatment. After the course in the hospital, and the ambulatory regimen for 30 days thereafter, the patient is advised to take 2 teaspoonfuls of colloidal aluminum hydroxide after each meal, and at bedtime. The stringency of the diet is relaxed somewhat, but the patient is warned to avoid coarse food and condiments and to eschew alcohol and tobacco.

It has been impossible to keep in touch with all the patients who received the intensive course of treatment with colloidal aluminum hydroxide in the hospital. However, 30 have been followed closely for 2 years or more (4 for 3 years), in order to determine whether the prolonged administration of colloidal aluminum hydroxide would prevent the recurrence of peptic ulcers. All of them have taken colloidal aluminum hydroxide regularly during this period. Twenty-six in the group had duodenal ulcer, and 4 had gastric ulcer.

The patients reported once a month for examination and advice. At the end of 2 years, none had had any recurrence of symptoms, and roentgenograms showed no evidence of new lesions in the stomach or duodenum. Several of these patients, prior to the treatment, had had a recurrence of symptoms about two or three times annually for a number of years.

It is to be noted, however, that since these patients were examined so regularly, they were being continually reminded to adhere to the recommended diet, and this factor cannot be overlooked in considering their freedom from recurrences. On the other hand, some of them had been conscientious and meticulous previously in following dietary and other prescribed treatment, and still had not been free from ulcer symptoms for a comparable period.

To determine whether daily doses of colloidal aluminum hydrox-

ide given over such a prolonged period produced any undesirable effect, complete laboratory studies were carried out on each of the 30 patients. The blood was analyzed for chlorides and carbon dioxide-combining power; no disturbance of the acid-base balance of the blood was indicated. Gastric analysis with histamine showed that the gastric acidity was approximately normal in all cases. Sigmoidoscopic examination of each patient showed no evidence of irritation of the lower bowel. The urinalysis showed no deviation from normal.

Summary. An experience in the management of peptic ulcer by means of the continuous administration of colloidal aluminum hydroxide extending over 3 years, and including the treatment of 407 patients, furnishes convincing evidence that this method has definite advantages over other forms of therapy in this disease. The treatment represents no radical departure from previous methods, but controls gastric acidity more effectively because of the use of a more efficacious neutralizing agent, which is administered continuously instead of intermittently. By the continuous administration of colloidal aluminum hydroxide, both day and night, the delicate granulation tissue formed in the process of healing is not destroyed by accumulation of acid. In addition to its exceptional neutralizing effect, colloidal aluminum hydroxide appears to promote healing by coating the lesion with a jelly-like, protective mass, and by its astringent effect.

The most striking features of this treatment are: 1, the prompt relief of pain in all cases (within 24 hours); 2, the rapid healing of the ulcer (in 7 to 10 days, according to roentgenograms); 3, the healing of refractory ulcers in patients who had tried other methods of treatment, without success; and 4, the excellent results in cases of bleeding ulcer. Of 101 patients with massive hemorrhage treated, only 3 died.

It is not claimed that this regimen can prevent the recurrence of ulcers, after they have been healed. Nevertheless, 30 patients who have continued to take colloidal aluminum hydroxide by mouth for 2 years or more, have been followed closely throughout the entire period, and none of them has had a recurrence, although a number of them previously had had an exacerbation of ulcer symptoms two or three times annually, for several years. Laboratory studies made on these patients showed that the drug had no harmful effect, even when administered for prolonged periods.

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FIG. 1.—Case 1. An ulcer niche defect and spastic constriction of the lower esophagus is shown at arrow *A*, the herniated cardia of the stomach at *B*, and the diaphragm at *C*.

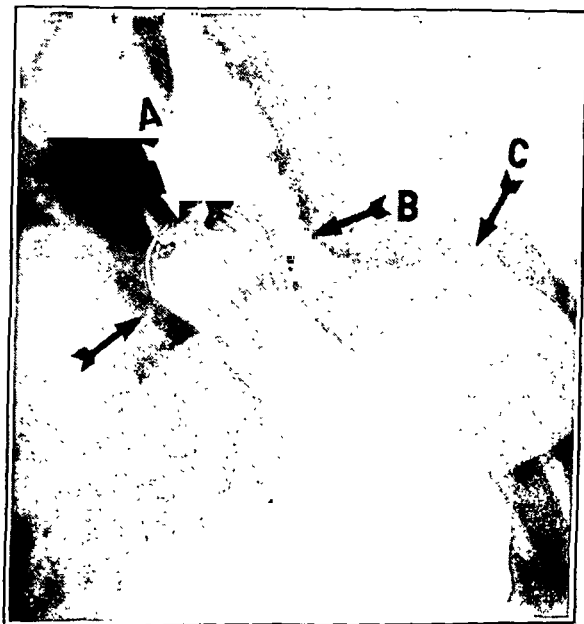


FIG. 2.—Case 2. An ulcer niche defect and spastic contraction of the lower esophagus is illustrated at arrow *A*, the herniated cardia of the stomach at *B*, and the diaphragm at *C*.

PEPTIC ULCER OF THE LOWER ESOPHAGUS ASSOCIATED WITH ESOPHAGEAL HIATUS HERNIA. REPORT OF 2 CASES.

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DIAPHRAGMATIC hernia of the cardia of the stomach through the esophageal opening occurs with greater frequency than a review of the literature would indicate. Numerous reports of this subject abound in the more recent literature. The incidence of esophageal hiatus hernia vary from 0.02 to 1.2%.² This form of hernia may be complicated by anemia hemorrhage, diverticula of the esophagus, cardiospasm, stricture of the esophagus, peptic ulcer of the esophagus, carcinoma of the esophagus or stomach, gastric and duodenal ulceration.

The coëxistence of gastric ulcer with esophageal hiatus hernia has been reported in many instances. However, a large number of cases of unexplained anemia, associated with this condition are recorded, many of which have been explained as being due to congestion. Bock, Dulin and Brooke report 10 cases of secondary anemia associated with hiatus hernia, 3 of which had abdominal explorations and 2 others came to autopsy. They found no lesions to account for the bleeding, except a marked congestion of the mucous membrane, caused by increased venous pressure.

In this communication, 2 cases of peptic ulcer of the esophagus associated with esophageal hiatus hernia are presented. In perusing the available literature, I have been unable to find a similar report of the coëxistence of peptic ulcer of the esophagus and hiatus hernia.

Case Reports. CASE 1.—Mrs. I. B. H., aged 46, complained of difficulty in swallowing for 6 months. The esophageal distress was markedly increased on eating solids, but she also experienced some discomfort in taking liquids. Regurgitation occurred immediately after swallowing, but there was no vomiting. Bowels were regular; stools dark in color, showed evidence of blood. There was some loss of weight and a secondary anemia. Roentgenologic gastro-intestinal studies revealed a definite retardation of the barium meal in the lower end of the esophagus. A persistent constriction and a small persistent ulcer niche defect in the constricted area was observed (Fig. 1). The cardia of the stomach is prolapsed through the esophageal opening of the diaphragm. The hernia being of the sliding variety, reduced itself on change of position. The lower esophagus is seen anteriorly and in front of the herniated cardia. The curvatures of the stomach appeared normal and regular in contour; the pylorus filled well; duodenal bulb was regular, did not reveal any signs of ulcer. The remaining intestinal tract showed nothing abnormal.

Roentgen impression: peptic ulcer of lower end of esophagus, with a spastic constriction which retarded the descent of the barium meal. Hernia of the cardia of the stomach through the esophageal hiatus of the sliding variety.

CASE 2.—Mrs. H. C. C., aged 68, complained of having had a hemorrhage 6 weeks ago. She now complained of epigastric distress and discomfort on swallowing, substernal burning and regurgitation, but no vomiting. Stools have been black in color, examination of which showed evidence of blood. There was a marked secondary anemia, with loss of weight. Roentgen examination of the gastro-intestinal tract showed a persistent constriction in the lower esophagus, with a small irregular transient fleck of barium, which was repeatedly observed under the fluoroscope after each swallow of the opaque medium. These findings were observed in two separate examinations (Fig. 2). The cardia of the stomach was herniated through the esophageal hiatus of the diaphragm. The hernia was of the permanent type, which did not slide back into the abdomen on change of position. The contour of the stomach curvatures were regular, the pylorus and duodenal bulb filled well, showed no evidence of ulceration; the colon was dilated and atonic, but emptied normally following an enema.

Roentgen Impression. Peptic ulcer of lower end of esophagus associated with a persistent type of hernia of the cardia of the stomach through the esophageal hiatus of the diaphragm.

Summary. Two cases of peptic ulcer of the esophagus associated with esophageal hiatus hernia are roentgenologically demonstrated. The possibility of peptic ulcer of the esophagus associated with hiatus hernia being a causative factor in the production of anemia should be considered. In a review of the available recent literature, no instance of the coëxistence of peptic ulcer and hernia have been found.

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ACUTE PUERPERAL HYPOPHYSEAL NECROSIS.

WITH REPORT OF A FATAL CASE.

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ACUTE necrosis of the anterior lobe of the pituitary gland in parturient women, although uncommonly encountered, has received some attention recently. Last year Sheehan,⁸ of the Glasgow Royal

Maternity Hospital, reported 11 such cases in which death followed delivery within a period of 14 hours to 30 days. A short time after this a similar case came to our attention. Because of the relative infrequency of such reports and the peculiar symptom complex exhibited by the patient we wish to make this brief report.

Mrs. A. C., aged 43, married, white, Gravida I, at term was referred by the family physician to Dr. Eder's service at the Cottage Hospital. A routine history disclosed that she had suffered no serious previous illnesses. She had undergone a tonsillectomy in 1929. Her menstrual periods began at 13, occurred regularly every 28 days, were of the usual duration and amount, and were accompanied by some cramp-like dysmenorrhea. When first seen by her family physician, 6 weeks before term, the patient weighed 131 pounds, the urine showed no albumin and the blood pressure was 159/92. One week later the urine showed a trace of albumin. Two weeks before admission the blood pressure had risen to 162/92 and the urine still showed a trace of albumin. She had lost 1 pound in weight. Her prehospital medication consisted of citrocarbonate and phenobarbital.

On the day of hospital admission her blood pressure was 184/108 and the urinary albumin was 2+. Labor began at 6 A.M., shortly before admission. Examination revealed an apparently full term pregnancy. The pelvic measurements were normal. There was some edema of the ankles and a peculiar brown discoloration of the skin. Labor progressed slowly with irregular shallow contractions. The cervix became fully dilated and effaced after 14 hours of labor. The fetal head was just below the mid-pelvis in O. L. A. position. During the ensuing 2 hours in spite of somewhat stronger contractions no progress was apparent, and in view of the hypertension and albuminuria it was deemed wise to interfere. Under nitrous oxide and ether vapor anesthesia a lateral episiotomy was done and a healthy baby was delivered in O. L. A. position by low mid-forceps at 10.15 P.M. after something over 16 hours of labor. The soft parts were lacking in elasticity and the episiotomy was extended by a spontaneous laceration along the left vaginal wall. There was considerable bleeding from the laceration and it was immediately repaired. Numerous attempts to express the placenta were unsuccessful. The patient was sent to bed with the placenta retained but with no bleeding. At midnight, 1½ hours later, the patient suddenly became pulseless and blood pressure could not be ascertained. After receiving stimulants and immediate glucose in saline followed by acacia and blood intravenously she recovered rapidly and the placenta was expressed with some difficulty. The blood loss at delivery and placental extraction was not over 700 cc. She received 2 blood transfusions following her placental extraction. For the next 12 hours her condition seemed good and she com-

plained only of headache. Her abdomen then became distended and she began to vomit. No abdominal tenderness or rigidity was noted. Late the second day postpartum her vomiting and abdominal distention were relieved by a Lavine tube and the bowels began to move well. Her general condition, however, was not good. Her pulse remained about 120 and the temperature rose from 100 the first day postpartum to 103 the third and fourth. She was restless and complained of headache, became mentally confused and on one occasion got out of bed. On the third day postpartum, in spite of intravenous solution and ephedrine, the systolic pressure stayed below 90. Readings on the fourth and last day postpartum were 60/30, 90/65, 75/30, 50/20, 55/25, 90/48. She became drowsy and cyanotic and died 93 hours after delivery. Her fluid intake was above 4000 cc. per day and the urinary output was 1700 cc., 6120 cc., 5780 cc. and 1400 cc. on the successive days after delivery. The blood picture on the last day was R.B.C., 4,100,000; Hb., 82%; W.B.C., 15,000.

Postmortem Examination ($\frac{1}{2}$ hour after death). External examination: The body is that of a well-developed middle-aged white woman. The skin has a faint, yellowish-brown color apparent equally on all surfaces. The breasts are full and nipples are slightly excoriated. The abdomen shows slight diastasis of the lower rectus muscles. There is scant subcutaneous fat and the tissue hydration is good. Incision: Y-type, serous cavities negative. Heart: 290 gm., negative. Lungs: Right, 215; left, 175 gm., negative. Gastro-intestinal tract: Shows the colon distended moderately with fluid. Liver: 2100 gm. Scattered beneath a thin capsule are irregular yellowish mottled areas. Section shows these to be scattered at random through the liver substance. The lobular units are visible. The cut surface is dark and bloody. Spleen: 250 gm., firm and dark. Kidneys: Right, 155 gm.; left, 140 gm., both similar. The capsule strips with ease. The cortex and medulla are of good thickness. The renal pelves are slightly hemorrhagic. The ureters are slightly dilated. Uterus, tubes and ovaries: The tubes are injected and edematous and the ovaries small and soft. The uterus measures 25 by 15 by 10 cm. Its endometrium is shaggy and is covered by a layer of clotted blood 1 cm. thick. Smear of the endometrium and tubal mucosa shows Gram-negative and Gram-positive diplococci. Pancreas: 100 gm. normal. Adrenals: Negative. Lymph nodes and skeleton: Negative. Brain: 1150 gm. negative. Pituitary: Weight, 1 gm. It is softened and has a yellow color. (Necrosis at this time was not suspected.) Cerebral vessels are soft and dilated.

Bacteriology: Blood culture negative.

Microscopic. Heart, lung, stomach, spleen, kidneys, negative. Liver: Dilatation of the central venules with blood is noted but the

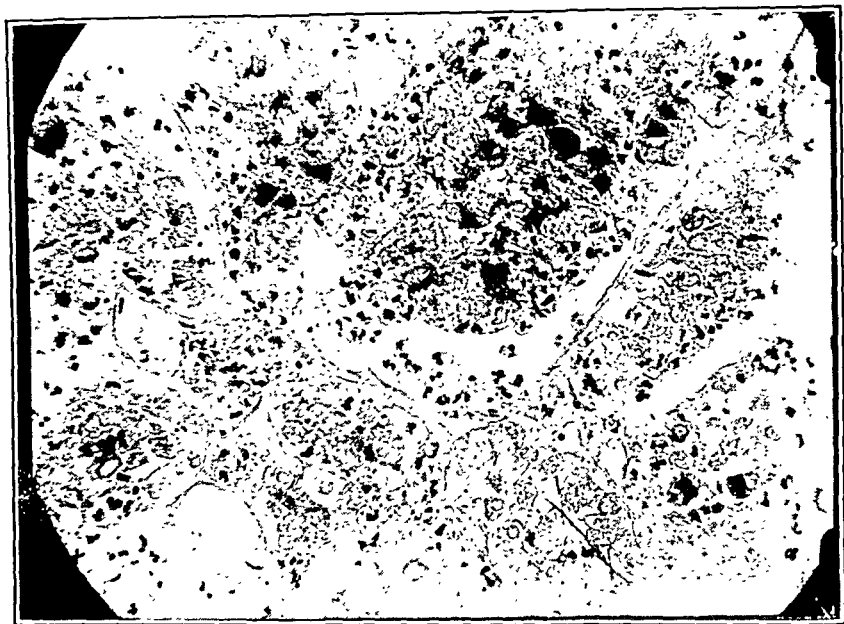


FIG. 1.—The cellular detail is lost. There is a focus of coagulation necrosis in the center. Polymorphonuclears infiltrate the necrotic cells. Fibrin is deposited at the lower edge of the section. ($\times 400$ —Mallory's phosphotungstic acid hematoxylin.)

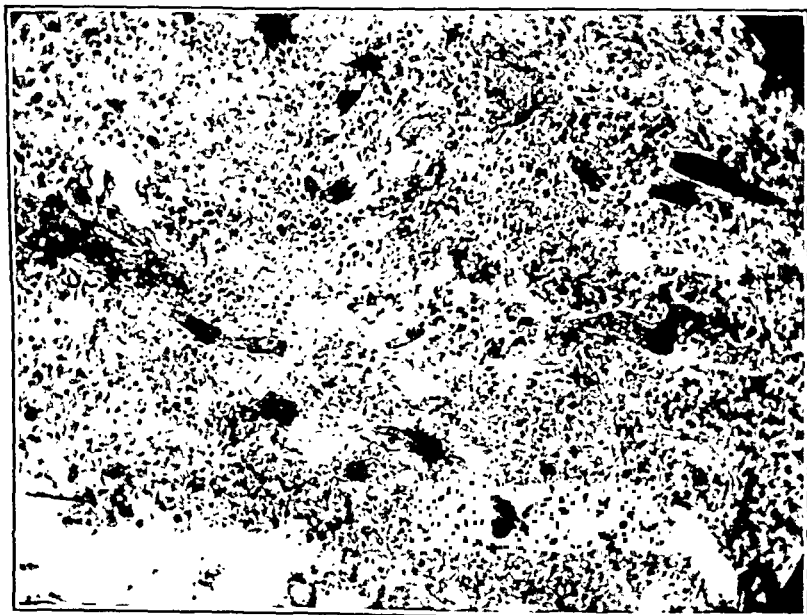


FIG. 2.—The alveolar structure of the hypophysis is lost. The gland cells stain poorly. Hyaline and fibrin thrombi fill the sinusoids. ($\times 180$ H. and E.)

liver cells remain intact. Uterus: Many of the distended cavernous vessels of the endometrium are filled with red thrombi. The fibrin coating on the endometrial surface is infiltrated with neutrophils. The muscle fibers are hypertrophied and indistinct. Ovary and pancreas: Negative. Adrenal: The cortex is of good thickness. The outer cortical cells are vacuolated and appear intact throughout. The medulla is thin but is otherwise negative. The adrenal does not fall into any of the exhaustion types as outlined by Zwemer.¹⁰ Section of voluntary muscle is negative. Brain: Sections of the brain stem, medulla and cerebrum show moderate perivascular edema only. Pituitary: In the pars anterior all cells stain poorly and are blurred. Only occasional nuclei can be differentiated from their homogeneous amorphous eosinophilic cytoplasm. Some cells are darker than others, suggesting that they are basophils, but necrobiosis has progressed to the stage where cell identification is hazardous. Polymorphonuclear neutrophils occupy many cavernous channels and invade areas of frank gland cell necrosis (Fig. 1). A few minute foci of apparently intact cells remain. Numerous hyaline and fibrin thrombi are noted in the vascular sinusoids (Fig. 2). The endothelium of these channels does not appear viable at points of thrombosis. The appearance of the gland is one of infarction. Gram stain fails to show any bacteria in the section. Only one piece of the pituitary was cut. The remainder of the gland was assayed for adrenotropic and gonadotropic hormones by Dr. Bischoff. Neither of these could be demonstrated. The absence of gonadotropic hormone is very significant inasmuch as small amounts of this have been found to be easily assayable. The microscopic sections do not include the posterior pituitary.

Discussion. In his excellent review (1937)* of some 60 cases of acute anterior pituitary necrosis collected from the literature, Sheehan⁸ points out that the greatest number with massive involvement occurred postpartum. A similar association was noted by Simmonds⁹ in the condition of chronic hypophyseal insufficiency which bears his name. The mechanism of the necroses occurring at or just after delivery is in some question. The theory of embolism advanced by many previous authors cannot explain the majority of cases, particularly those without endocardial disease or embolic residua elsewhere. The concept of thrombosis of the vascular channels in the gland due to both local and general conditions is on firmer ground. Changes in the blood at the puerperium such as increased fibrinogen content and platelets favor such a hypothesis. Postpartum hemorrhage with retained placenta should augment the coagulability of the blood. The prompt puerperal involution of the pituitary as detailed by Erdheim and Stumme⁴ would

* In view of the availability of this recent and excellent review it has not been deemed desirable to discuss the literature on this subject.

seem to favor vascular thrombosis locally, as well as the effect of ischemia from shock and syncope occurring at delivery on the vascular endothelium of the gland. Puerperal infection has been noted prior to the pituitary change in only a portion of the cases of acute necrosis reported, so that this factor does not seem essential to the incidence of thrombosis.

Prominent signs and symptoms which appeared during our patient's postpartum course were nausea and vomiting, headache and hypotension. Ileus could explain the first symptoms. Recourse to the pituitary to explain the headache and hypotension has some appeal. Local hypophyseal inflammation could account for the headache. The extreme hypotension occurring on the fourth day after her delivery, when the erythrocytes numbered over 4 million per mm. and when no sign of hemorrhage was present, certainly finds difficulty in explanation from the standpoint of shock, especially since the amount of fluid (glucose, saline and blood) administered intravenously was more than sufficient to maintain blood volume. A large urinary output would not be expected if the condition were due to shock. The assumption of a pituitary origin of her hypotension seems preferable to that of shock.

A certain amount of clinical evidence is at hand concerning the association between pituitary insufficiency and hypotension. Cushing³⁶ has pointed out that pressure on the hypophyseal stalk from tumor with resulting partial anterior lobe necrosis was associated frequently with unmistakable degrees of hypotension, in one case 85/50, in another 60/50. Houssay⁵ quotes similar cases associated with tumors of the hypophysis. He recognizes also the possibility of hypotension resulting from posterior lobe hypofunction but states that in the rat, dog and human it probably reflects a deficiency of the anterior lobe. In 1932, Calder¹ discussing Simmonds' disease raised the question of whether hypotension and asthenia were incident upon pituitary insufficiency directly or secondarily upon adrenal insufficiency. Assuming the hypotension to be glandular in our case, the absence of adrenal change and the presence of morphologic and biologic pituitary insufficiency leaves us little choice but to implicate the pituitary directly.

The question may well be raised whether the pituitary necrosis was a coincidental or major factor in this woman's death. It seems unlikely that a sapremia from uterine and tubal infection of 3 days' duration was the main factor in her demise. The issue becomes one of whether the human can tolerate the sudden absence of pituitary function. It was shown after years of debate that the sudden and complete removal of the pituitary in laboratory animals did not cause death promptly in many of them. It is also known that almost complete destruction of the anterior lobe may be a chance finding at autopsy without clinical disturbance having been detected

during life (Krumbhaar⁶). Cushing's and Crowe's (*et al.*)^{2,3a} early experimental work indicated, however, that many of their hypophysectomized dogs developed loss of interest, irritability, anorexia, muscle twitching, lethargy, coma and death. Mahoney^{7a,b,c} noting the similarity between this syndrome and hypoglycemia showed that in both the dog and monkey these frequently fatal hypoglycemic accidents could be avoided by large amounts of glucose. We do not know whether our patient displayed this condition. She took small amounts of liquid nourishment by mouth for 2 days after delivery and received about 305 gm. of glucose intravenously during her puerperal course. The lack of other postmortem findings sufficient to explain this patient's rapidly fatal puerperal course, however, inclines us to assign major significance to the acute hypophyseal insufficiency known to be present.

Summary. 1. A case of acute thrombosis and necrosis of the anterior pituitary, terminating fatally during the puerperium, is reported.

2. The endocrine deficiency resulting therefrom is shown and its possible effects briefly discussed.

3. It is suggested that this may be a more common puerperal complication than is usually recognized, and that should the puerperal course of a patient progress unfavorably without obvious cause, blood sugar studies, active glucose therapy and anterior pituitary extracts might be in order.

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THE PROLONGATION BY ZINC SALTS OF A WATER BALANCE REACTION OF POSTERIOR HYPOPHYSEAL EXTRACT.*

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INTEREST in the effect of salts of zinc upon the activity of hormones has arisen from two lines of approach. The first of these

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was and is concerned with the action of various activating substances, by themselves inactive, upon hypophyseal, gonadotropic substances. In 1934, Maxwell⁶ found that zinc sulphate increased the gonadotropic function of pituitary extracts and advanced the idea that this was due to a decrease in the rate of absorption of the injected extract. Fevold, Hisaw and Greep⁴ found that zinc sulphate added to extracts containing the follicle stimulating hormone (F.S.H.) or follicle stimulating hormone (F.S.H.) plus luteinizing hormone (L.H.) produced ovaries in immature or hypophysectomized rats which weighed 2 to 3 times as much as in animals receiving the extract without the zinc. Similar results were obtained by Saunders and Cole.¹¹

The second line of approach came especially from the investigations of Scott and Fisher,¹² who noted that insulin containing 0.1% of zinc had a more prolonged hypoglycemic effect upon rabbits than insulin alone. These results were confirmed in patients with diabetes mellitus by Rabinowitch and his associates.^{5,7-9}

Dodds, Noble, Rinderknecht and Williams³ visualized from the above work the possibility that zinc salts may have a general prolonging effect upon the action of other hormones. They state that Rosenthal and Kamlet¹⁰ found that zinc prolonged the action of diphtheria toxin; but the paper to which they refer does not make this statement nor, indeed, is it concerned at all with zinc. Dodds *et al.*³ conclude that zinc prolongs the gastric secretion of hydrochloric acid produced by histamine in cats with gastric fistulae but their Figure 2 presented in exemplification does not indicate clearly the experimental basis of this conclusion. They further demonstrated that the addition of zinc acetate considerably prolongs the inhibition of water diuresis in rats by injection of extract of the posterior hypophysis.

The present investigation was designed to investigate the effect of salts of zinc added to posterior hypophyseal extracts and injected into frogs. Under such circumstances, posterior pituitary extracts themselves produce an uptake of water amounting to 15 to 25% of the weight of the animal in 3 to 4 hours at room temperature and this reaction is not identical to the inhibition of water diuresis in mammals.^{1,2} Zinc was found to prolong the retention of water so taken up and experiments were devised to elucidate the mechanism involved.

Method. The general procedure used was described by Boyd and Brown.¹ Leopard frogs (*Rana pipiens*) were placed in water in individual beakers, injected with 0.5 international units of pituitrin surgical* per 10 gm. body weight containing various amounts of zinc. The animals were weighed to the nearest 0.1 gm. before and at intervals of 1 hour after injection. From 6 to 24 frogs were used in each experiment with similar numbers as controls, (a) without pituitrin and (b) without zinc. The

* Supplied in generous quantities by Dr. E. A. Sharp, of Parke, Davis & Co.

experiments were performed in an open laboratory and in view of the finding of Boyd and Whyte² that insensible air currents in an open, ventilated room may cause appreciable evaporation of water from exposed skin of frogs in beakers, experiments were done to find means of preventing this. It was finally noted that if the frogs were almost completely immersed in water (200 cc. in a 400 cc. beaker) the uptake of water was practically the same whether the experiment was performed in a dark, unventilated room or in an open laboratory or whether or not beakers were covered with glass sheets instead of wire covers, which were criteria used by Boyd and Whyte² to study the dehydrating effect of insensible air currents. It is necessary to emphasize this detail in technique because, as shown by Boyd and Whyte,² failure to eliminate or take into consideration evaporation from such air currents is the probable explanation of discrepancies in the results of reports in the literature.

The Effect of Zinc Acetate on Intramuscular Injections of Pituitrin. Solutions of zinc acetate were prepared containing different amounts of zinc calculated as zinc and not as zinc acetate. The solutions were mixed in equal parts with fresh surgical pituitrin and 0.05 cc. of the resultant mixture were injected intramuscularly into frogs for each 10 gm. of body weight, this amount containing 0.5 international units of pituitrin. Other groups of frogs received the same amount of pituitrin combined with an equal amount of distilled water and a still further group received corresponding amounts of zinc with distilled water substituted for the pituitrin.

The results obtained in a number of typical experiments are listed in Table 1. In this work, in contrast to previous reports

TABLE 1.—THE EFFECT, ON WATER UPTAKE, OF ZINC (AS ZINC ACETATE) ADDED TO PITUITRIN AND INJECTED INTRAMUSCULARLY INTO FROGS.

Pituitrin per 10 gm. body weight, units.	Zinc added to pituitrin, %.	Number of animals.	Mean maximal uptake of water, %.	Time after injection of maximal uptake, hrs.	Duration of water retention, hrs.
Pituitrin without zinc.					
0.5	None	12	21.4	2.0	6.5
0.5	None	12	22.1	2.5	6.5
0.5	None	6	20.3	3.0	7.0
0.5	None	6	20.4	2.5	7.0
0.5	None	6	17.8	3.0	7.5
0.5	None	6	20.8	2.5	8.0
0.5	None	6	19.3	2.5	8.0
0.5	None	12	22.9	2.5	8.0
0.5	None	12	23.4	3.0	8.5
Pituitrin with zinc.					
0.5	0.01	6	17.8	2.0	7.0
0.5	0.02	6	17.8	2.0	7.0
0.5	0.08	6	17.2	3.5	9.0
0.5	0.1	6	18.8	3.0	9.5
0.5	0.1	12	24.8	3.0	10.0
0.5	0.1	12	21.7	3.0	10.0
0.5	0.4	8	18.1	3.0	13.0
0.5	0.6	6	23.2	2.0	15.0
Zinc without pituitrin.					
None	0.08	6	1.1	3.0	5.0
None	0.1	6	2.2	1.5	5.0
None	0.1	24	2.2	2.5	6.0
None	0.2	6	6.2	1.5	9+
None	0.4	6	5.3	1.5	10+

from this laboratory,^{1,2} interest centered chiefly on the length of time frogs retained water taken up as a result of injecting pituitrin. In preliminary trials, the time required for the weight of the frog to return to exactly the initial weight was found to be extremely variable. In fact, it was found that the weight of normal, uninjected frogs in water may vary from hour to hour by as much as $\pm 3\%$. The impression was gained that the normal equilibrium between the water inside and outside the frog may be in a constant state of flux and vary within these limits. Hence it was decided to accept as the end-point of the effect of pituitrin the time when the weight of the frog had decreased to within 3% of the initial and such values are included in the extreme right-hand column of Table 1 (except figures for the group "Zinc Without Pituitrin" where duration means the hours required to come back to the initial weight $\pm 0.05\%$).

When pituitrin alone was injected, the end-point of the reaction occurred in from 6.5 to 8.5 hours in the different groups, on the average. Zinc added to a concentration of less than 0.08% had no effect upon the duration of water retention but concentrations of zinc above 0.08% definitely prolonged the retention. The optimum concentration of zinc was found to be 0.1% , and this amount prolonged water retention by an average of one-third the normal time. Zinc had no effect upon the height of the reaction, *i. e.*, it did not affect the maximal uptake of water, although it may have slightly deferred the time at which the peak occurred.

Concentration of zinc greater than 0.1% caused an even greater prolongation of the reaction, but such doses became increasingly more toxic. This was evidenced by an uptake of water by those frogs receiving zinc alone, an uptake which was in excess of the normal variation in weight of 3% . Such water was retained for a long time, many animals being found to have held it for over 24 hours. With concentrations of zinc less than 0.2% there was no appreciable effect upon the weight of the animal from the zinc itself. When a concentration of 0.4% zinc was used (20 mg. of zinc per kilo or about one-fifth of the lethal dose per kilo by mouth in man), many animals became and remained water-logged and sluggish and the average mortality was 33% . The mortality rate increased until, when 2% of zinc was used, all animals died.

It may be concluded from these experiments that the addition of 0.1% of zinc to pituitrin prolongs the retention of water taken up by frogs when pituitrin is injected intramuscularly. Lesser concentrations of zinc become progressively less active and greater concentrations progressively more toxic.

Is the Effect Due to Zinc or to the Negative Ion? Studies under this heading were made of the comparative effect of several salts of zinc and demonstrated that all water-soluble salts which were examined were equally efficacious providing that the negative radicle

was not toxic in the dose used. The zinc salts studied were the acetate, chloride, nitrate, sulphate, bromide, iodide, permanganate and sulphocarbolate (phenolsulphonate), all of which were added in equal parts to pituitrin surgical to produce a final mixture containing 0.1% of zinc as zinc. All salts prolonged the water retention over pituitrin alone by 20 to 60%. The first 4 were non-toxic as far as could be seen from no change in body weight or physical activity of the animals, but control animals receiving zinc alone showed an appreciable increase in weight with all of the last 4 salts named which were hence considered toxic in this dose.

The Site of Injection. Dodds *et al.*³ state that intravenously injected zinc mixtures do not exhibit zinc-prolonging action and conclude that zinc acts by retarding absorption of the hormone when injected into tissues. This idea was examined by injecting zinc-pituitrin mixtures (a) intramuscularly, (b) subcutaneously and (c) into the dorsal lymph sac. From a total of 18 experiments, each with 6 to 12 frogs given the mixture, an equal number receiving pituitrin alone and another equal number receiving zinc alone, it was found that zinc was most effective when given intramuscularly, less so given subcutaneously and practically without effect when injected into the dorsal lymph sac. These results lend support to the conception that zinc salts act in some manner upon tissues at the site of injection, probably by retarding absorption of the hormone.

Is There a Reaction Between Zinc and Pituitrin? The alternative explanation of the effect of zinc is that it may combine chemically or physically with the water balance principle in pituitrin forming a substance which is either more slowly absorbed or has a more prolonged action. This suggestion was studied in four ways:

1. If the pituitary principle combines with zinc and if this hypothetical reaction is a slow one, then allowing zinc and pituitrin mixtures to stand for varying periods should produce more of the hypothetical zinc-pituitrin compound and hence injections of such mixtures should give increasingly more effective prolongations. Such was not the case. When pituitrin was combined with 0.1% of zinc (zinc acetate used in this and subsequent work) and immediately injected, the effect was just as good as when the zinc pituitrin mixture was allowed to stand in the icebox for periods up to 21 days.

2. A chemical reaction should be augmented by heat, so mixtures of pituitrin and zinc were made and boiled for periods up to 15 minutes, adding regularly hot distilled water to keep the mixture to its original volume. Boiling for this period was found to have no effect upon the reaction of pituitrin itself in frogs, nor did it increase the effectiveness of the zinc-pituitrin mixtures.

3. A proposed chemical reaction between zinc and pituitrin may have an optimum pH. The pH of mixtures of zinc and pituitrin was altered by adding varying amounts of Sörenson's phosphate

mixtures, sodium hydroxide, hydrochloric acid, nitric acid and glacial acetic acid and mixtures were injected intramuscularly with a pH from 2.6, which was below the normal pH of zinc acetate and pituitrin (4.2), to as high as 7.6, at and above which zinc tended to precipitate out of solution. Zinc prolonged the action of pituitrin the same amount at all hydrogen-ion concentrations. There does not appear to be any need to neutralize zinc-pituitrin mixtures as described by Dodds *et al.*³

4. If zinc and the pituitary factor combine chemically, such a reaction might be lessened by diluting the medium in which it is proposed that the reaction occurs. Mixtures of zinc acetate (0.1%) and pituitrin were diluted 1, 2 and 3 times with equal parts of distilled water. Such diluted mixtures gave results identical to the undiluted mixture.

These results provide no evidence that zinc combines in any way with the pituitary principle to produce a new substance which has a more prolonged action on water retention in frogs.

Does Zinc Combine With Tissue Protein to Delay Absorption of Pituitrin? The conception advanced by Maxwell⁶ and re-stated by Dodds *et al.*³ that zinc prolongs hormonal reactions by retarding tissue absorption of the active principle at the site of injection was investigated in two further ways in addition to the experiments on the site of injection described above.

1. It is well known that zinc precipitates protein and hence it appeared that adding a solution of protein to zinc-pituitrin mixtures might enhance the effect when injected into the dorsal lymph sac, at which site zinc ordinarily has little effect. Such combinations were made of equal parts of the zinc-pituitrin mixture and of blood plasma of guinea-pigs with controls receiving plasma alone, pituitrin alone and zinc plus pituitrin. The results were not particularly striking but when injected into the dorsal lymph sac, the mixture of plasma-zinc-pituitrin prolonged the retention of water for an interval 15% longer than zinc-pituitrin or pituitrin alone, both of which again gave identical results. The plasma had no appreciable effect by itself in the amount (0.05 cc.) used nor did it alter the effect of subcutaneously or intramuscularly injected pituitrin.

2. If zinc is injected intramuscularly alone, it should immediately combine with tissue protein and if pituitrin be subsequently injected into the same site it should have: (a) a typical prolonging effect if zinc binds pituitrin to muscle, or (b) no prolonging effect if pituitrin must first combine with zinc. A needle was injected into frog muscle and zinc injected; 1 minute later pituitrin was injected with a second syringe into the same site through the same needle which had meanwhile been left *in situ*. A typical prolonged water retention was obtained.

These experiments support the view that zinc prolongs the pituit-

rin effect in frogs by binding pituitrin at the site of injection in tissue and prolonging its absorption rather than by combining with pituitrin to form a new substance.

Summary. The addition of 0.1% of zinc, in the form of a suitable salt, to pituitrin injected into frogs prolongs the retention of water taken up by them. Lower concentrations of zinc are progressively less active and greater concentrations are progressively more toxic. All water-soluble salts of zinc investigated, which were not toxic at this dose, had the same effect. Evidence is presented favoring the view that the effect of zinc is upon the tissues at the site of injection rather than by the formation of a new compound between zinc and the active principle in pituitrin.

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THE CHOICE OF TECHNIQUE FOR THE SEDIMENTATION TEST.

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IN the 20 years since the red cell sedimentation test was introduced by Fahraeus, a voluminous literature has appeared and considerable confusion has arisen due to the multiplicity of methods by which this originally simple test has been carried out (see Pinner, Knowlton and Kelly⁹). Many of the proposed newer methods aim only to simplify the originally very simple and practical technique of Westergren, which is favored by Fahraeus, but it is doubtful if much can be achieved in this direction. On the other hand, some authors believe that the simpler sedimentation procedures, of which the Westergren method is typical, have inherent defects which can be eliminated by modifications in the technique, and they have proposed methods which aim to overcome these defects and thus to yield more accurate results. Usually it has been on theoretical

grounds that these modifications have been advanced. The aim of this paper is to examine the validity of these claims, and to determine whether the simpler sedimentation methods are really defective, and lead in many cases to inaccurate results.

The chief criticisms^{11,12} made against the Westergren and similar methods are as follows:

1. Dry citrate or oxalate lowers the sedimentation rate, while heparin does not influence the sedimentation rate.

2. Citrate or oxalate solution has a still more pronounced effect in lowering the sedimentation rate.

3. Due to cell volume variation in different blood samples, the citrate concentration in the resultant plasma must vary, and this will influence the sedimentation rate.

4. It is the maximum uniform sinking velocity of the red cells, and not the 1-hour reading, which expresses the essential result of the test. Related to this is the claim that graphic methods of presenting the results of the test, for example the Cutler technique,³ give valuable information which is lost when only the 1-hour reading is taken.

5. The Westergren method does not correct the observed sedimentation rate for the effect of red cell volume or cell count.

Before examining these claims, it is well to keep in mind that all of the numerical scales, in terms of which the sedimentation rate has been recorded, are arbitrary ones. If two methods of performing the sedimentation test are equally satisfactory and reliable, there should exist a consistent relation between the results obtained by these two methods, though this relation may take the form of a curve, and not of a straight line, when plotted as a graph. But either scale of results would be equally satisfactory in clinical practice. This is important since it will be pointed out that the statement "dilution with citrate alters the sedimentation rate" may imply only that a *definite and consistent* change is introduced into the numerical results of the test, *e. g.*, the number of millimeters sedimentation in 1 hour. Where this is the case the sedimentation rate results obtained on citrated blood are as accurate and reliable as results obtained by some other method, and the objection to the use of citrate is unfounded.

1. *Effect of Dry Citrate or Oxalate Upon the Sedimentation Rate.* It is generally accepted that small amounts of heparin can be used as anticoagulant without affecting the sedimentation rate. A comparison of the 1-hour sedimentation rates, using heparin and dry oxalate as anticoagulants, was made by Wintrobe and Landsberg,¹⁵ who found that the use of oxalate did not retard the sedimentation rate.

When heparin is used as anticoagulant, there is usually a longer delay before a uniform sedimentation rate is reached, while with citrated or oxalated blood, sedimentation commences more promptly.

Hence a fair comparison of the relative effects of heparin, citrate and oxalate upon the sedimentation rate can best be made by measuring the "uniform sinking velocity," *i. e.*, the velocity of sedimentation during that intermediate phase when it is assumed that neither the preliminary delay for aggregation of the red cells, nor the final delay due to packing of the cells in the lower part of the tube, are operative.*

The method employed to make this comparison was as follows: to duplicate 2 cc. portions of blood from each of 27 persons was added 1 drop of heparin solution (150 mg. to 1 cc. water) or 1 drop of 35% sodium citrate solution; the drops of heparin or citrate solution were of approximately the same size, about 0.022 cc. After cooling to room temperature and well mixing, the samples were transferred by capillary pipettes to Wintrobe type sedimentation tubes, giving blood columns 100 mm. high and 4 mm. diameter. Readings, estimated to the nearest 0.1 mm. were taken at 2-minute intervals and the uniform sinking velocity was measured from the graph of each sedimentation.

The data obtained are plotted in Figure 1, and show that no significant change in sedimentation rate is produced by using citrate in place of heparin. The correlation coefficient is 0.97 ± 0.01 .

The contention that certain electrolytes under certain conditions can influence the suspension stability of blood is beyond question. But with the specific electrolytes in question, *i. e.*, dry oxalate or citrate, and in the concentrations actually employed, the evidence quoted above indicates that they produce no significant effect upon the sedimentation rate.

2. *Effect of Isotonic Oxalate or Citrate Solution Upon the Sedimentation Rate.* If an isotonic oxalate or citrate solution is employed as anticoagulant, instead of the dry salt, another factor is introduced; the blood plasma is diluted, and this lowers the concentration of those substances which increase the sedimentation rate. Hence this factor tends to lower the sedimentation rate. On the other hand, dilution with oxalate or citrate solution tends to accelerate the sedimentation rate by reducing both the percentage of red cells, and the viscosity and specific gravity of the plasma. The sum total of these effects, as found by experiment, is given in Figure 2, which is taken from Figure 8 of Westergren's article.^{13b} This figure compares the 1-hour readings, in the Westergren sedimentation tube, of undiluted citrated blood (*i. e.*, blood drawn into a syringe slightly moist

* Most authors interpret the period of uniform sedimentation to indicate that the red cell aggregates reach a maximum and constant size, and then settle with a velocity which is an expression of Stokes' law, provided allowance is made for the proximity of other aggregates. This view needs to be qualified. As sedimentation proceeds, the red cell aggregates in the lower part of the tube are brought closer together, and this alone retards sedimentation long before complete packing of the cells occur, for, as Lundgren⁸ puts it, the aggregates in the upper part of the tube tend to lean upon those below. Lundgren finds that the red cell aggregates increase in size throughout the test, and the period of uniform sinking velocity is merely that phase during which any increase in velocity due to increasing size of aggregates is offset by the retarding effect due to their increasing proximity.

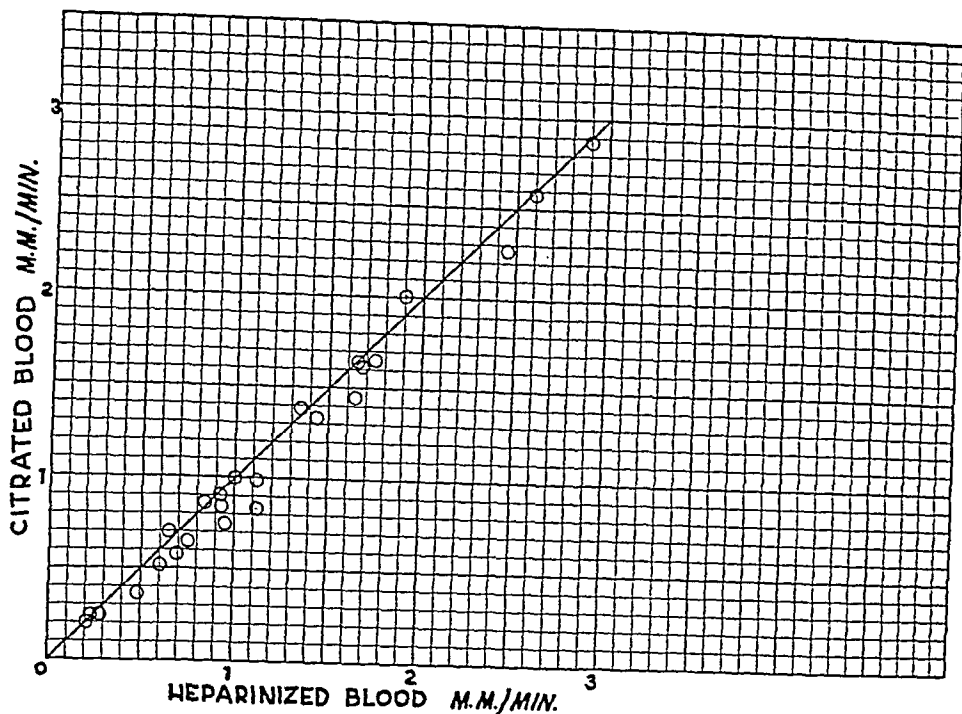


FIG. 1.—Comparison of the uniform sinking velocities of undiluted heparinized blood and undiluted citrated blood.

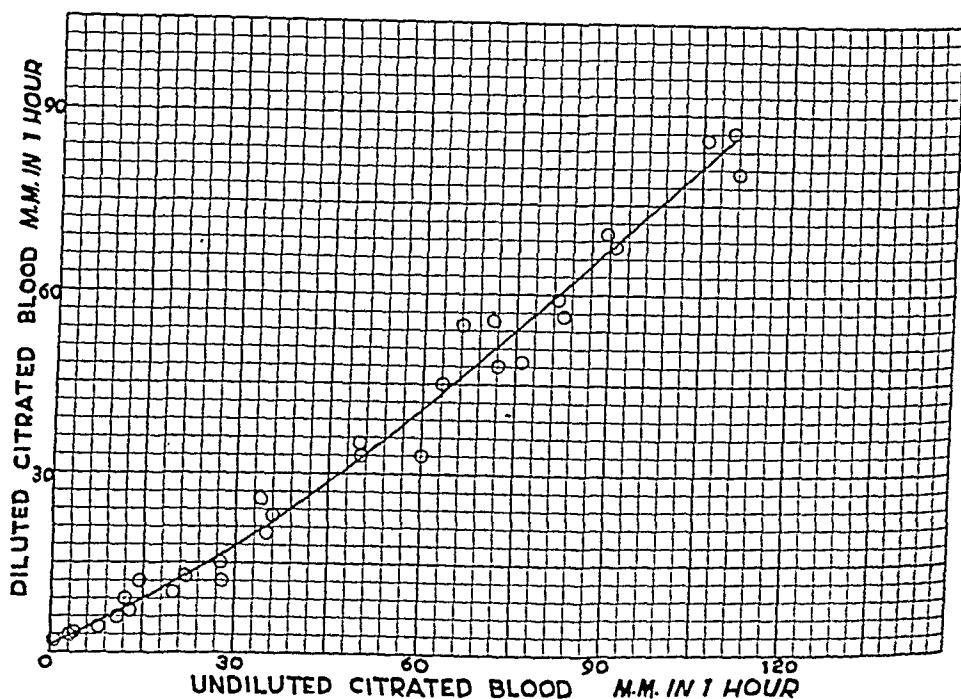


FIG. 2.—Comparison of the 1-hour sedimentation distance, in the Westergren sedimentation tube, of diluted and undiluted citrated blood. (After Westergren.)

with 30% citrate) with diluted citrated blood (4 vols. blood to 1 vol. 3.8% citrate). Allowing for the curvilinear relationship, the correlation coefficient is 0.95 ± 0.014 . In Figure 3 are given the data obtained here of the relative sinking velocities, mm. per minute in the Wintrobe sedimentation tubes, of undiluted heparinized blood and of diluted citrated blood (85 vols. blood to 15 vols. of 3.8% citrate). This graph shows a correlation coefficient of 0.96 ± 0.01 . In each case a consistent relation is found to exist for all types of blood, normal or pathologic, between the sedimentation rates on undiluted blood and on blood containing 15 or 20% of citrate solution. The statement that "dilution with citrate affects the sedimentation

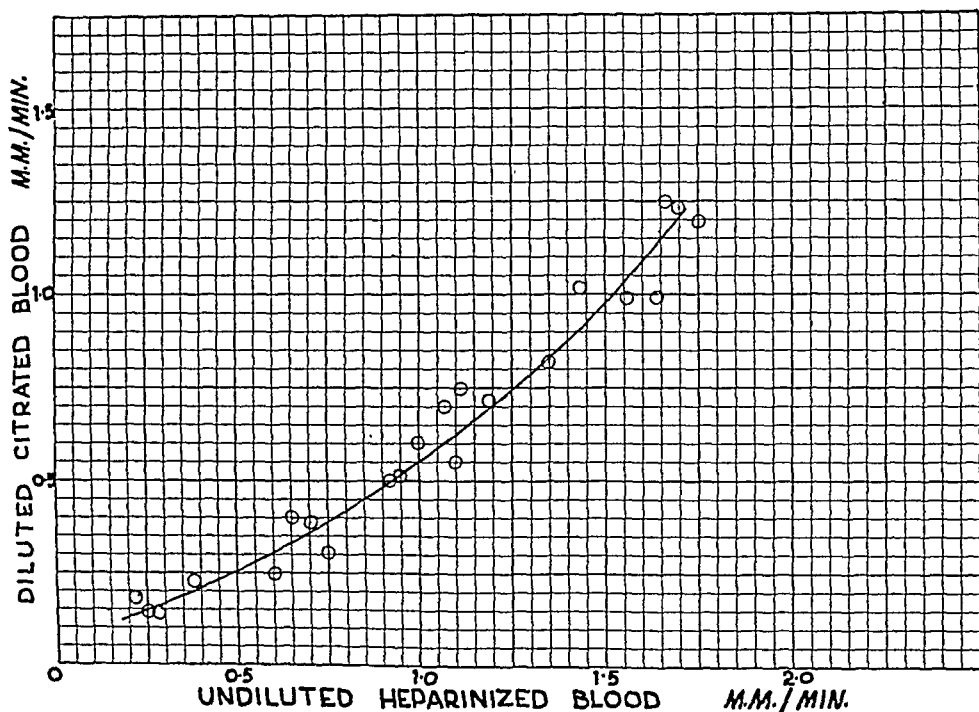


FIG. 3.—Comparison of the uniform sinking velocities of undiluted heparinized blood and diluted citrated blood.

rate" is misleading unless it is recognized that while the numerical results of the sedimentation test are modified, this change in the scale of results is a consistent one, and hence gives a satisfactory scale in terms of which to denote sedimentation rates.

3. *Effect of Varying Citrate Concentration in the Plasma.* It has repeatedly been pointed out that when blood and citrate solution are mixed in constant proportions, the citrate concentration in the resultant plasma is not constant, but varies according to the percentage red cell volume of the blood. Any changes of the sedimentation rate as a result of this are probably due to differing degrees

of dilution of the plasma, rather than to citrate concentration *per se*. However that may be, this criticism of the use of citrate solution as anticoagulant does not apply to the results of the Gram⁵ or Hambleton-Christianson⁶ methods, in which the results are simultaneously corrected for this factor and for the effect of cell volume. The results obtained by other methods which employ citrate as anticoagulant, *e. g.*, those of Westergren, Cutler and Linzemeier, should theoretically be influenced by the varying citrate concentration in the plasma. Westergren^{13b} investigated this point, but his data show that regardless of whether blood is of high or low cell volume, the sample after dilution with citrate solution gives a sedimentation rate bearing a consistent ratio to that of the undiluted blood. Apparently this factor of dilution produces no clinically significant effect upon the sedimentation rate.

4. *Use of the Single 1-hour Reading in Place of the Uniform Sinking Velocity.* From a theoretical standpoint, as Lundgren,⁸ Fahraeus,⁴ and Rourke and Ernstene¹¹ point out, it is preferable to measure the uniform sedimentation velocity rather than to take the 1-hour reading. In the case of undiluted heparinized blood it seems that no consistent relation exists between the 1-hour sedimentation distance and the uniform sinking velocity; due to this fact, Rourke and Ernstene were unable to prepare, from the 1-hour sedimentation rates upon heparinized blood, uniform curves to correct for the effect of cell volume. But with blood containing 15 or 20% by volume of 3.8% citrate solution, a consistent relation exists between the 1-hour reading and the uniform sinking velocity. This relation, as determined in 50 consecutive blood samples from patients in this tuberculosis sanatorium, using blood containing 15% citrate solution, and placed in the Wintrobe type sedimentation tube, is shown in Figure 4. These samples were taken without reference to age, sex, or extent or type of disease. Samples which settle 50 mm. or less in 1 hour show an almost straight line relationship between the 1-hour reading and the uniform sinking velocity, and over this range the correlation coefficient is 0.98 ± 0.01 . This type of tube has a blood column only half as long as that in the Westergren tube, and due to packing at the bottom of the tube, variations in cell volume influence the 1-hour reading when this is greater than 50 mm.; this prevents the existence of a consistent relationship above this figure.

A similar comparison of the 1-hour reading to the uniform sinking velocity was made by the Westergren technique, using blood samples from 39 patients. The results are given in Figure 5, and these also show a good correlation, the coefficient being 0.97 ± 0.01 .

Westergren^{13b} states that in some cases of jaundice associated with some other disease which gives a high sedimentation rate, there is an unusually long aggregation period before uniform sedimentation commences; Westergren, Theorell and Widström¹⁴ state that pos-

sibly abnormal lipoid factors in the blood may lead to rare sedimentation curves of this type. However, no such instance has been encountered in the 100 patients covered in this work.

When blood samples containing 15 to 20% by volume of isotonic citrate solution are placed in sedimentation tubes giving blood columns of 100 or 200 mm. length, the data given in Figures 4 and 5 indicate that the 1-hour reading provides the significant information concerning the sedimentation rate. To measure the uniform sinking velocity requires considerable time from the operator, and gives essentially the same result, expressed in a different numerical scale.

The Cutler Technique. This method has come into rather wide use, but the data presented above do not justify the claims made for it. A short sedimentation tube (50 mm. blood column) is employed in the Cutler technique;³ readings are taken every 5 minutes or so, and plotted on a graph. Results are then expressed in 3 terms: *a*, the 1-hour sedimentation; *b*, the "sedimentation time," *i. e.*, the time until packing of the cells at the lower part of the tube reduces the sedimentation rate to 1 mm. in 5 minutes; and, *c*, the visual appearance of the graph.

The objection to this method is that results are expressed in a confusing manner. The true characteristic of the sedimentation test is the uniform maximum settling velocity.⁸ As pointed out and illustrated in Figures 4 and 5, with citrated blood in tubes of 100 to 200 mm. length, a single 1-hour reading gives essentially the same data as the uniform sinking velocity. But in the short Cutler tube, the 1-hour reading is markedly influenced by the packing of the cells at the bottom of the tube, if the blood samples have a moderately fast settling rate. The defect of the Cutler technique is that the tubes employed are too short. If rapidly settling blood is placed in these short tubes, then as Cutler states, the 1-hour reading is perhaps the least important observation that can be made. But this remark is not true for the longer Westergren tube, with which the 1-hour reading gives the clinically significant data. Except for the slowly settling bloods, the end result of the Cutler test cannot be given by a single figure, but is some function of the three factors recorded—sedimentation distance, sedimentation time, and visual appearance of the graph. Thus the interpretation and comparison of results from the Cutler technique is more difficult than is the case with the clean-cut results of the Westergren method.

5. *Correction for the Effects of Cell Volume, Cell Count or Hemoglobin Content.* In our present state of knowledge, there is no justification for correcting the observed sedimentation rate for the effects of cell volume, cell count or hemoglobin content. All such methods of correction are based on *in vitro* findings, when the ratio of cells to plasma is artificially changed. In practice other factors are involved^{4,13b}

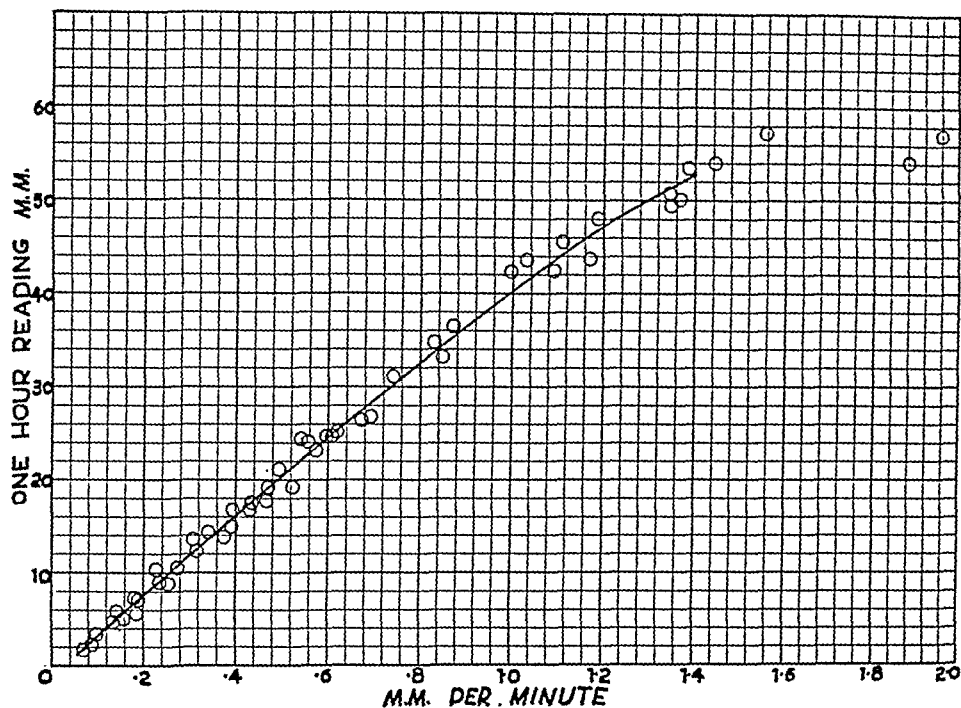


FIG. 4.—Comparison of the uniform sinking velocity to the 1-hour sedimentation distance of citrated blood in the Wintrobe sedimentation tube; 100 x 4 mm. blood column.

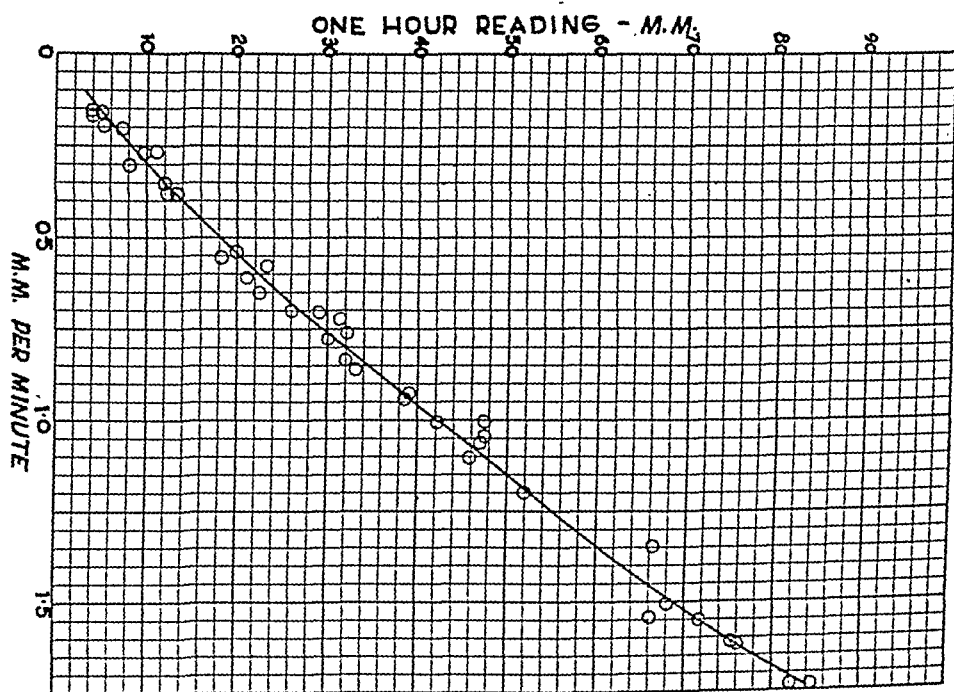


FIG. 5.—Comparison of the uniform sinking velocity to the 1-hour sedimentation distance of citrated blood in the Westergren sedimentation tube; 200 x 2.5 mm. blood column.

and there is evidence that when corrections are made to the sedimentation rate, greater errors are introduced than those which are avoided.^{7,13b,14} The data obtained at this sanatorium² from a comparison of corrected and uncorrected rates to the clinical condition of the patients support this view; in fact, correcting the sedimentation rate on the basis of the *in vitro* effects of cell volume, and so on, irrespective of the technique employed, at times leads to results which are clinically absurd.

A Comparison of the Results of the Rourke-Ernstene Technique¹¹ With Those of a Simpler Method⁶ Employing Citrate as Anticoagulant. The aim of the Rourke-Ernstene sedimentation technique is to avoid the use of citrate; results are given in terms of the uniform sinking velocity, after correcting for cell volume. If the data presented in this article are correct, simpler methods of performing the sedimentation test, using citrate as anticoagulant, should yield essentially the same result as the Rourke-Ernstene technique, although the results will be expressed in terms of a different numerical scale.

A comparison of results from the Rourke-Ernstene technique and from the the Hambleton-Christianson⁶ technique was made on duplicate blood samples taken from each of 55 patients. The results (Fig. 6) indicate that a fairly consistent relation exists between the results of the two methods, the correlation coefficient being 0.92 ± 0.02 . In no case did the results suggest that the Rourke-Ernstene technique gave more valuable information than was obtained by the other method.

In the case of one patient (W. J. M.), the results of the two methods did not have the anticipated relation to one another. The results of three successive tests are indicated in Figure 6,* as in all cases the C. S. R. by the Rourke-Ernstene technique is much lower than would be expected from results with citrate as anticoagulant. Dr. B. J. Robinson kindly furnished the following details of the patient.

Case Abstract. "W. J. M., farmer, aged 28, tuberculosis of 1 year's duration, with fatigue, loss of weight, frequent small hemoptyses, cough and expectoration. On admission, patient had definite bilateral lung involvement, apex to fourth anterior rib on both sides, with excavation in right upper lobe. Sputum positive. Bilateral pneumothorax established, with fairly select upper lobe collapse on each side. No great change in symptoms observed. A recent examination fails to show any appreciable lesions as far as the lung is concerned. Sputum is positive by concentration test. The prognosis is poor."

* In all three tests the *observed* S. R.'s, whether with citrate or heparin as anticoagulant, remained much more constant. The wider differences in the *corrected* S. R. results shown in Figure 6 are due to changes in cell volume, and these corrected results do not correspond to the condition of the patient, which remained relatively unchanged. This is an example where correction for cell volume is a disadvantage, and leads to results which are of less value.

The sedimentation rate obtained when using citrated blood is in better accord with this patient's condition than is the lower sedimentation rate indicated by the Rourke-Ernstene technique.

Use of Oxalate in Place of Citrate. Some workers prefer to use oxalate in place of citrate as anticoagulant. The disadvantage of oxalate, whether used dry or in isotonic solution, is that the sample should be used within 1 hour of drawing the blood,¹ whereas citrated blood retains its sedimentation rate unchanged over a period of 4 or 5 hours. If dry oxalate or citrate is used as anticoagulant in place of isotonic oxalate or citrate solution, (1 vol. to 4 vols. of blood), the numerical results of the test are altered to the extent indicated in Figure 2 of this article.

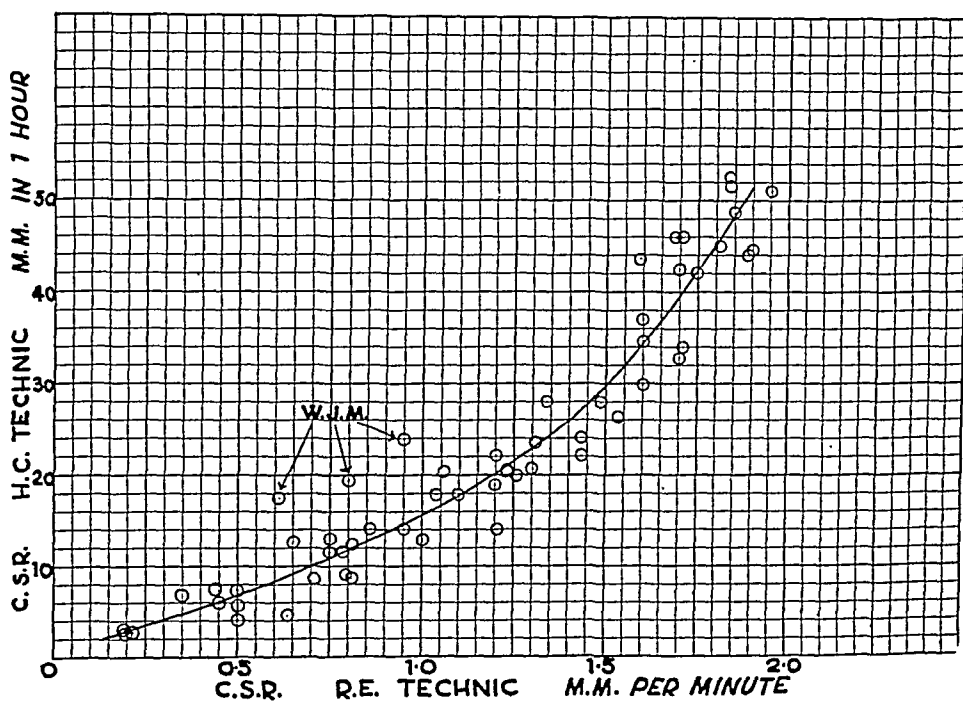


FIG. 6.—Comparison of the C. S. R. by the Rourke-Ernstene method to the C. S. R. by the Hambleton-Christianston method.

Summary. The data obtained at this tuberculosis sanatorium indicate that the sedimentation test remains today essentially what it was when Fahraeus introduced the test in 1918, and that all the significant clinical data which may be obtained by sedimentation procedures can be found by a single 1-hour reading by the Westergren technique. Alleged improvements upon the Westergren sedimentation method have been presented which appear theoretically correct, *e. g.*, correction for cell volume, the use of heparin in place of citrate, and graphic methods of recording the results. Instead of making

the test more valuable, these changes have the reverse effect, either by leading to results of less clinical value, or by making the test more tedious to perform or less clear to interpret without increasing its clinical value. Hence it is recommended that the Westergren method, by reason of its simplicity, reliability and priority, should be adopted as the standard method of performing the sedimentation test.

In conclusion, those who use the Westergren technique should keep in mind that due to the narrow bore of the tube it is all the more important to see that the tubes are perfectly vertical during the test.¹⁰

The authors are indebted to Dr. D. W. Crombie, Medical Superintendent, at the Queen Alexandra Sanatorium, and Dr. J. L. Blaisdell, Director of the Morgan Laboratory, for their interest and coöperation in this work. The technical assistance of Mr. R. Comrie is also acknowledged.

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NOTE ON ERYTHROBLASTIC SPLENOMEGALY OCCURRING DURING PREGNANCY.

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EXTRAMEDULLARY erythropoiesis occurs in association with certain diseases of the bone marrow, such as erythroblastic anemia¹ and carcinomatous replacement of the bone marrow;⁴ but it is unusual to find hematopoietic foci in the spleen, liver and lymph nodes without conspicuous disease of the bone marrow. Emile-Weil, Isch-Wall, Perles and Seemama² have reported 4 cases that they term cryptogenic erythroblastic splenomegaly. The patients

were adults; 2 had anemia and 2 slight polycythemia. The total leukocyte count varied from 4400 to 29,000, with from 6.5 to 15% of myelocytes. Puncture of the spleen and liver showed many megakaloblasts and normoblasts, while puncture of the bone marrow revealed only a slight preponderance of normoblasts.

The present case with autopsy is described in order to define more accurately the morphological alterations of the condition. It also is the first case reported during pregnancy.

Case Report. A colored woman (No. 143468), aged 20, was first admitted to the Prenatal Clinic of the New York Lying-in Hospital on July 3, 1936. The expected date of confinement was November 28, 1936. The past history was negative except for frequent attacks of rheumatic fever.

On the first admission, with a normal 5-months' pregnancy, the physical examination was negative. Hemoglobin was 74% and the Wassermann test, negative. In view of a former positive Wassermann test, a total of 3.15 gm. of arsphenamine and 0.2 gm. of bismuth were administered during the succeeding month.

Between September 5 and 19, 1936, the patient suffered from a lobar pneumonia involving the left lower lobe. Hemoglobin was 60%, and white blood cells 25,000, with 63% neutrophils and 10% myeloblasts. The cell volume was 23%. Type XVIII pneumococcus was cultured from the sputum. With symptomatic treatment and a transfusion there was an uneventful recovery.

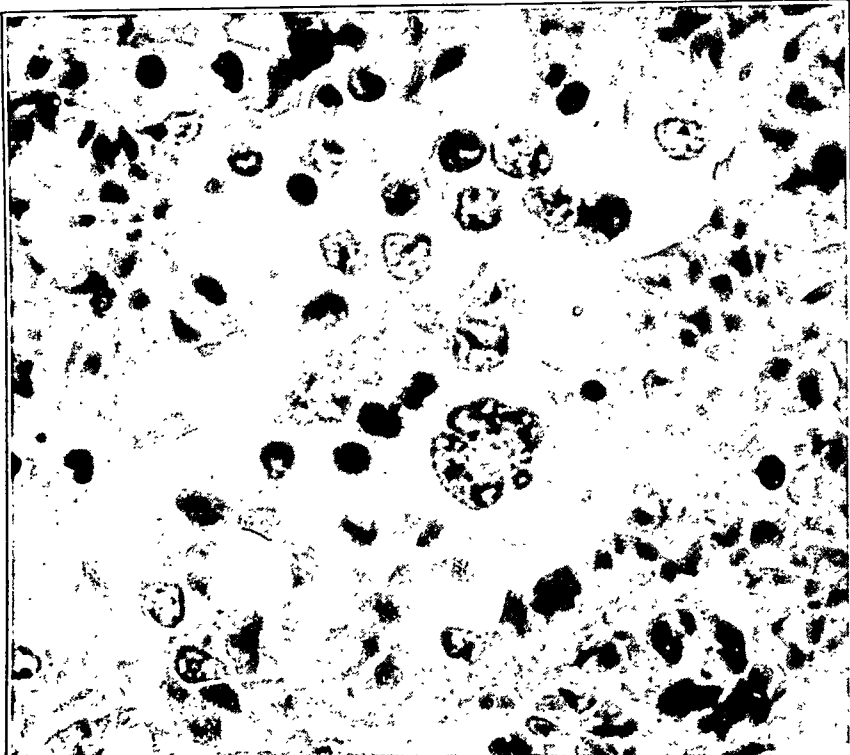
The patient was readmitted to the hospital on October 24, 1936, because of frequency of urination, dysuria, and blood-tinged urine for a period of 24 hours. No abnormality was found by physical examination. Hemoglobin was 70%, red blood cell count 3,040,000, white blood cell count 8480. The urine showed 3+ albumin and numerous red blood corpuscles. Upon the basis of intravenous pyelograms and cystoscopic examination a diagnosis of subacute cystitis was made. Under irrigation treatment the amount of blood in the urine gradually diminished.

Labor began at 6 A.M. on November 16, 1936. The cell volume at this time was 27%. Progress was satisfactory, but the patient was so unco-operative and excitable that she was given morphine sulphate 0.010 gm. and scopolamine 0.0001 gm. on one occasion and rectal ether (90 cc. of ether and 0.6 gm. quinine) on two occasions.

After 15 hours of labor the patient delivered spontaneously by vertex presentation a normal female infant weighing 3000 gm. The third stage was normal and the placenta was delivered by the Schultze mechanism 8 minutes later with a measured loss of blood of 100 cc. An episiotomy was repaired without difficulty and the patient received nitrous oxide and oxygen anesthesia with 15 cc. of ether. At 10.15 P.M., or 1 hour after delivery, the pulse was 76 but feeble, and the blood pressure could not be obtained. The pulse then rose to 120 and was of poor volume. She was restless and had to be restrained. The skin was warm. At 10.50 P.M., the pulse was 148 and the respiratory rate 68. The only complaint at this time was epigastric pain. Examination of the heart and lungs was negative. There was no evidence of internal bleeding. In spite of intravenous therapy and cardiac and respiratory stimulants the condition did not improve. A transfusion was started at 12.42 A.M., but 7 minutes later respirations ceased, 3 hours and 30 minutes after delivery.

Autopsy. The body was that of an adult colored female. The breasts were well developed. A small quantity of bloody fluid issued from the vagina.

1



2

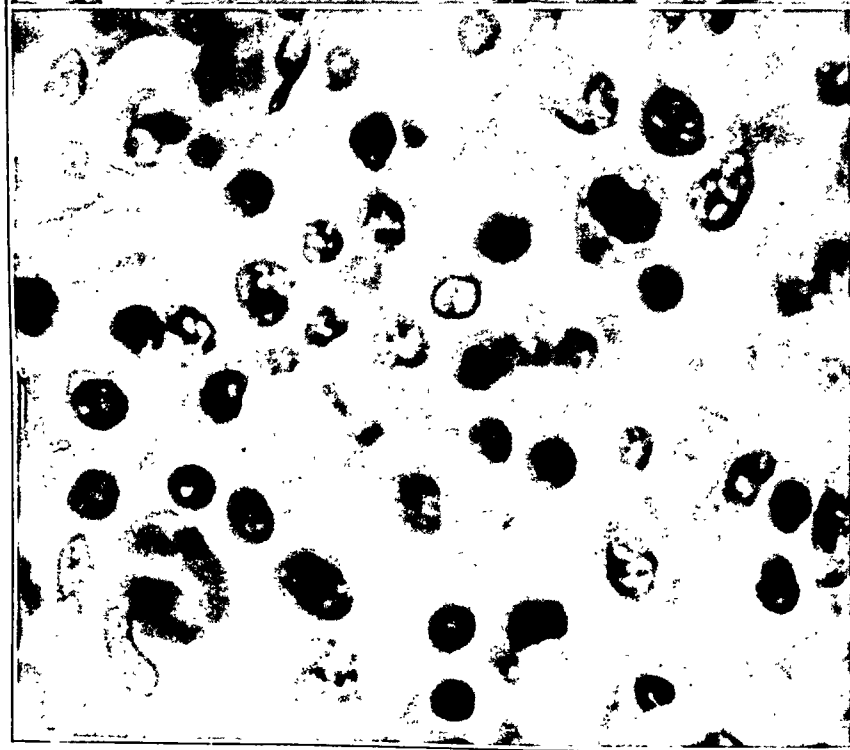


FIG. 1.—A small focus of erythroblastic tissue in the spleen. There are erythroblasts, megaloblasts and one megakaryocyte. ($\times 850$.)

FIG. 2.—Infiltration of a lymph node with immature myeloid cells. ($\times 1100$.)



The superficial lymph nodes of the axillary, cervical and inguinal groups were enlarged and soft. The cut surface was pinkish gray and finely granular. The visceral lymph nodes of the mediastinal, periaortic and mesenteric groups were of a similar appearance. The bone marrow of the vertebral bodies was reddish gray, of the ribs and sternum red, and of the mid-tibia reddish gray with little visible fat.

The spleen weighed 1190 gm., was firm in consistency and grayish red in color. The Malpighian bodies were indistinct and the pulp bulged slightly from beneath the capsule.

There were fibrous pleural adhesions laterally and posteriorly over both lungs but none over the apices. The lungs were crepitant throughout except for an area 2 cm. in diameter in the left lower lobe where the tissue was firm, gray and granular. There was a linear fibrous scar, 20 by 4 by 4 mm., in the right upper lobe. All of the tracheobronchial lymph nodes on the right side and the left inferior group contained caseous nodules which varied from 2 to 6 mm. in diameter. Roentgen ray examination revealed a calcified nodule in the left lower lobe and in a left inferior bronchial lymph node.

The liver weighed 2650 gm., was brown in color and firm in consistency. On section, the architecture was clearly visible as yellowish brown portal areas and reddish brown central areas.

The cortices of the kidneys contained numerous small abscesses. The pelves were slightly dilated, and the mucosa of the pelves, ureters and bladder was congested and swollen.

The uterus was large and the wall thickened, but there were no changes not characteristic of a 6-hour postpartum uterus. The tubes, ovaries and vagina were normal. The pituitary gland weighed 900 mg.

A smear of the blood in the hepatic veins showed many myeloblasts and myelocytes, together with normal cellular elements. There were no nucleated red blood cells. A culture of the spleen remained sterile after incubation for 7 days.

Microscopic Examination. The white pulp of the spleen is relatively decreased in amount. The red pulp is relatively increased, largely due to distention of the sinusoids with red blood cells. There is no increase in the reticulum or endothelial cells. Throughout the red pulp there are small foci composed of two cell types (Fig. 1). One is a small cell, 8 to 10 microns in diameter, with a round, hyperchromatic, dense nucleus and a narrow rim of acidophilic cytoplasm. Rarely there is more abundant cytoplasm and the nucleus is less chromatic. The second is a larger cell, 12 to 18 microns in diameter, round or polygonal, with a light staining vesicular nucleus and abundant, lightly acidophilic or neutrophilic cytoplasm. A few of the latter cells have from 2 to 3 nuclei. Occasionally these two kinds of cells are present in the same focus. They are interpreted as stages in the development of the red blood cells, the first as the normoblast and normocyte, and the second as the megaloblast. Scattered throughout the red pulp, usually not associated with the cellular foci, there are large cells, 50 to 60 microns in diameter, with four to eight hyperchromatic central nuclei. These cells are interpreted as megakaryocytes.

The lymph nodes throughout the body show conspicuous edema and congestion. The follicular architecture is entirely obliterated, and the blood-vessels are congested. The reticulum fibers of the tissue cords are separated and the interstitial spaces partially filled with lymphocytes, a moderate number of myelocytes and a few myeloblasts, normoblasts and megaloblasts (Fig. 2). Occasionally the erythrocytic elements are collected in small foci but the myelogenic elements are diffusely distributed. There is a rare multinucleated giant cell of the megakaryocytic type.

The individual liver cells are separated from one another but the cyto-

plasm and nuclei are normal in appearance. The sinusoids are narrow and filled with red blood cells and a few myelocytes and neutrophils. There is an occasional erythrocytic focus similar to those in the lymph nodes and spleen.

In the bone marrow of the tibia, vertebral bodies, ribs and sternum, there is a slight increase of erythrocytic and myelogenic tissue, but there are no atypical cells and no evidence of delayed maturation. In none of the hematopoietic organs is there pigmentation nor evidence of phagocytosis of red blood cells.

The lungs show an organizing pneumonia in the right lower lobe and a few tubercles in the left lower lobe. The kidneys show no pathologic change other than the abscesses described. The blood-vessels of the lungs and kidneys are dilated and filled with red blood cells and many myelocytes.

Sections of the placenta show a few immature myeloid cells in the maternal vessels. The cells in the fetal vessels of the placenta are normal.

Pathologic Diagnosis. Anemia; slight hyperplasia of the erythrocytic and myelogenic elements of the bone marrow; splenomegaly; hepatomegaly; erythrocytic foci in the spleen, liver and lymph nodes; myeloid infiltration of the lymph nodes; leukostasis of immature myeloid cells in the vessels of the lungs, kidneys, and liver; organizing pneumonia of the left lower lobe; pleural adhesions; postpartum uterus; hypertrophy of the pituitary gland; hypertrophy of the breasts; cystitis; ureteritis; pyelonephritis with multiple abscesses; congestion of the liver, spleen and kidneys; fibrous scar of the right upper lobe; conglomerate tubercles in the right lower lobe; fibrocaseous tuberculous nodules of the tracheobronchial lymph nodes; calcified tuberculous nodules in the right lower lobe and tracheobronchial lymph nodes.

Discussion. The essential alteration of the hematopoietic tissue is an enlargement of the spleen, liver and lymph nodes with the formation of erythrocytic foci. The changes resemble those of myeloid leukemia, erythrocytic anemia of Cooley and pernicious anemia; but there are structural changes or other factors entirely inconsistent with each of these diseases. The case in its essential features corresponds with those reported by Emile-Weil and his associates,² although the autopsies in their cases are so incompletely described that an exact comparison cannot be made.

The pathogenesis and etiology of the changes cannot be definitely outlined and must await study of additional cases. In the present case there are several factors which may be significant. During pregnancy the metabolism of iron is increased and the occurrence of anemia is more common than in non-pregnant women.³ An additional slight disturbance of the erythrocytic tissue might therefore result in conspicuous alterations. There is abundant evidence of infection in the present case: a lobar pneumonia 2 months before death, latent pulmonary tuberculosis, urinary infection with multiple abscesses of the kidney, and a history of repeated attacks of rheumatic fever. The history of a positive Wassermann test is of doubtful significance because of the absence of anatomical changes of syphilis. It is possible that one or more of the infections, combined with pregnancy, induced the alterations of the hematopoietic tissue.

Summary. A case of conspicuous extramedullary erythropoiesis with splenomegaly but without significant alteration of the bone marrow is reported. It was associated with lobar pneumonia during pregnancy but there is insufficient evidence to determine the etiology and pathogenesis.

We wish to thank Dr. Eugene L. Opie and Dr. Jacob Furth for assistance in the study of this case.

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SEDIMENTATION RATES OF SICKLED AND NON-SICKLED CELLS FROM PATIENTS WITH SICKLE CELL ANEMIA.

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ABUNDANT work has shown that there is a definite correlation between the tendency of erythrocytes to form rouleaux and their sedimentation rate.^{1,2} It has also been demonstrated that the proportion of red blood cells to plasma influences the rate of settling; and this has led to the practice, followed by many, of "correcting" the observed sedimentation rate when there exists a reduction below normal in the number of circulating erythrocytes.^{5,7} The material presented below is of interest because wide variation in the speed of settling of red cells of the same blood has been produced without altering their relative number. It was found that sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and in this condition did not sediment appreciably in one hour's time, whereas non-sickled cells from these same patients formed rouleaux and sedimented.

Method. The number of sickled erythrocytes in freshly drawn blood from patients with sickle cell anemia and the sickle cell trait was greatly increased by the well-known method of subjecting the blood to carbon dioxide.³ Five cc. of oxalated blood (4 mg. of potassium oxalate and 6 mg. of ammonium oxalate per 5 cc.⁷) were divided equally between 2 small Erlenmeyer flasks. The blood in 1 flask was subjected to a gentle stream of carbon dioxide for 1 or 2 minutes and the flask was then stoppered. The blood in the other flask was similarly treated with oxygen. Samples of blood from each flask were examined in wet cover glass and slide preparations for the per cent of sickled cells and for the presence or absence of rouleaux formation. One Wintrobe sedimentation tube was filled with

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each sample and sealed. Observations of the sedimentation of the erythrocytes were made at 5-minute intervals. Cell volume determinations were then made. The white cells did not separate in a distinct layer in the tube containing sickle cell blood which had been subjected to carbon dioxide, because there had been almost no sedimentation before the tube was placed in the centrifuge. For this reason, it was necessary to obtain the volume of packed white blood cells from the corresponding oxygenated tube; this value was then subtracted from the total volume of packed cells in the tube of blood treated with carbon dioxide to obtain the exact volume of packed red blood cells in that tube. No correction for anemia was made in any reading given below.

Results. The accompanying table contains data obtained with the blood of 2 patients with sickle cell anemia, 1 with the sickle cell trait, and a representative control. Similar results were obtained with blood from 2 other patients with sickle cell anemia. Subjecting of blood from these patients to carbon dioxide produced about 50% sickling, whereas less than 10% sickling was present when the same blood had been treated with oxygen. No rouleaux were observed to form in the blood treated with carbon dioxide and this blood sedimented less than 1 mm. in 1 hour; the oxygenated blood, on the other hand, formed good rouleaux and sedimented from 23 to 70 mm. in the same length of time.

TABLE 1.—SEDIMENTATION RATE OF SICKLED CELLS.

Patient:	Sickle cell trait.		Sickle cell trait.		Sickle cell anemia (quiescent).		Control (atrophic arthritis).	
R.B.C. per c.mm.:	2,810,000.		3,900,000.		Not done.		4,180,000.	
R.B.C. treated with:	O ₂ .	CO ₂ .	O ₂ .	CO ₂ .	O ₂ .	CO ₂ .	O ₂ .	CO ₂ .
Smear:	Rare sickled cells; field filled with rouleaux.	47% sickled; no rouleaux.	No sickled cells; good rouleaux formation.	53% sickled; no rouleaux.	9.5% sickled; few rouleaux, single cells and clumps.	45.5% sickled; no rouleaux.	Field filled with rouleaux; few single cells.	Field filled with rouleaux; few single cells.
Time (min.).	Sedimentation (mm.).		Sedimentation (mm.).		Sedimentation (mm.).		Sedimentation (mm.).	
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	6.0	0.0	1.5	0.0	0.0	0.0	0.0	0.5
10	19.0	0.0	9.5	0.0	1.7	0.0	1.0	1.7
15	33.0	0.0	18.0	<1.0	3.0	0.0	5.0	5.0
20	45.0	<1.0	25.0	<1.0	5.0	0.0	12.0	9.0
25	53.0	<1.0	31.5	<1.0	8.0	<0.5	22.0	14.2
30	59.0	<1.0	36.5	<1.0	10.0	<0.5	31.0	21.2
35	63.0	<1.0	42.0	<1.0	12.0	<0.5	35.5	29.0
40	66.0	<1.0	44.7	<1.0	14.0	<0.5	44.5	36.2
45	68.0	<1.0	48.2	<1.0	16.5	<0.5	48.7	40.5
50	69.0	<1.0	51.5	<1.0	19.0	<0.5	51.2	41.5
55	69.6	<1.0	53.8	<1.0	21.0	<0.5	52.7	47.0
60	70.0	<1.0	55.0	<1.0	23.0	<0.5	53.5	48.7
Vol. % packed red blood cells	20.3	27.3	26.0	31.6	22.0	25.0	35.0	35.0

Control determinations in addition to those presented in the table were made with blood samples taken from a normal individual, a patient with chronic glomerulonephritis, a patient with metastatic malignancy, and a patient with ulcers of the leg. No difference was detected between the appearance of the rouleaux in the samples subjected to oxygen and in those treated with carbon dioxide. The erythrocytes sedimented faster in the oxygenated tube by from 3 to 13 mm. in 1 hour; this result is consistent with that obtained by Ito.⁴

In all of the sickle cell and control bloods the volumes of packed red cells were consistently higher for the samples subjected to carbon dioxide than for those subjected to oxygen. It is well known that treatment of erythrocytes with carbon dioxide increases their volume.⁶

Summary. Sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and remained almost unsedimented after 1 hour's time, while non-sickled cells from the same patients formed rouleaux and sedimented.

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THE HEPATIC ORIGIN OF THE PLASMA-PROTHROMBIN OBSERVATIONS AFTER TOTAL HEPATECTOMY IN THE DOG.

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THE liver has been regarded as the site of formation of prothrombin, chiefly because certain hepatotoxic agents, chloroform, carbon tetrachloride and phosphorus, cause a plasma-prothrombin deficiency, and because some patients believed to have severe damage of the liver have failed to respond to substrates containing large amounts of vitamin K and bile salts. Williamson and Mann¹¹ pointed out that the use of hepatic toxins is an unreliable method for the study of the functions of the liver. Direct experimental evidence on the relation of the liver to prothrombin synthesis is conflicting. Dam, Glavind, Lewis and Tage-Hansen² found an increase in blood coagulability in geese following exclusion of the

liver from the circulation. Warner¹⁰ reported a moderate decline in plasma prothrombin concentration after partial hepatectomy in rats.

We have investigated the effect of total hepatectomy on the plasma-prothrombin concentration of the dog. Four dogs were hepatectomized by the three-stage method of Mann and 4 dogs by one-stage methods (Firor and Stinson,³ and Markowitz, Yater and Burrows⁷). Prothrombin determinations were made by the method of Quick.⁸ To estimate the effect of the associated drop in plasma fibrinogen on the prothrombin determinations a solution of fibrinogen prepared as described by Smith, Warner and Brinkhous⁹ was added to certain specimens of plasma before recalcification. Plasma fibrinogen determinations were carried out according to the method of Foster and Whipple⁴ on 5 of the dogs. To evaluate the effect of possible blood dilution, a very rough estimate of the hematocrit was obtained by centrifuging the oxalated blood in a No. 2 International centrifuge at 2000 r.p.m. for 10 minutes. The plasma-protein concentration was determined by the falling drop method of Barbour and Hamilton.¹

All of the animals, except 1 which lived only 2 hours and received a transfusion of normal blood before the final specimen was taken, showed a fall in plasma prothrombin concentration (see Table 1).

TABLE 1.—CHANGES IN PLASMA PROTHROMBIN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.).	Preoperative prothrombin (% normal).	Last prothrombin determination before death (% normal).	Decline from preoperative level (%).
379	Mann	6	80	10	87
877	Firor and Stinson	2	No prothrombin decline*		
891	Markowitz <i>et al.</i>	1	100	32 ±	68
892	Markowitz <i>et al.</i>	6	82	35	57
904	Markowitz <i>et al.</i>	5½	100	0	100
691	Mann	19	40	11	72
781	Mann	14	45	16	64
827	Mann	4	48	42†	12

Average 58

* Dog had transfusion shortly before last specimen.

† Last specimen 2 hours postoperatively.

The effect on fibrinogen was determined in 5 dogs and was much less pronounced (Table 2).

TABLE 2.—CHANGES IN PLASMA FIBRINOGEN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.)	Preoperative fibrinogen level (gm./100 cc. plasma).	Fibrinogen level before death (gm./100 cc. plasma).	Decline (%)
892	Markowitz <i>et al.</i>	5	0.508	0.407	20.0
904	Markowitz <i>et al.</i>	5½	1.019	0.400	61.2
691	Mann	19	0.297	0.229	22.9
781	Mann	14	0.805	0.779	3.3
827	Mann	4	0.511	0.226	55.8

Average 32.6

The curves obtained for prothrombin, fibrinogen, approximate cell volume, and plasma protein for the 2 animals that survived longest are shown in Charts 1 and 2. The relation of plasma prothrombin percentage, as determined with added fibrinogen, to prothrombin percentage without added fibrinogen, is shown in Chart 3. The 2 curves are very similar.

Dog 691
Changes in Prothrombin, Plasma Protein, Hematocrit
and Fibrinogen after Hepatectomy.

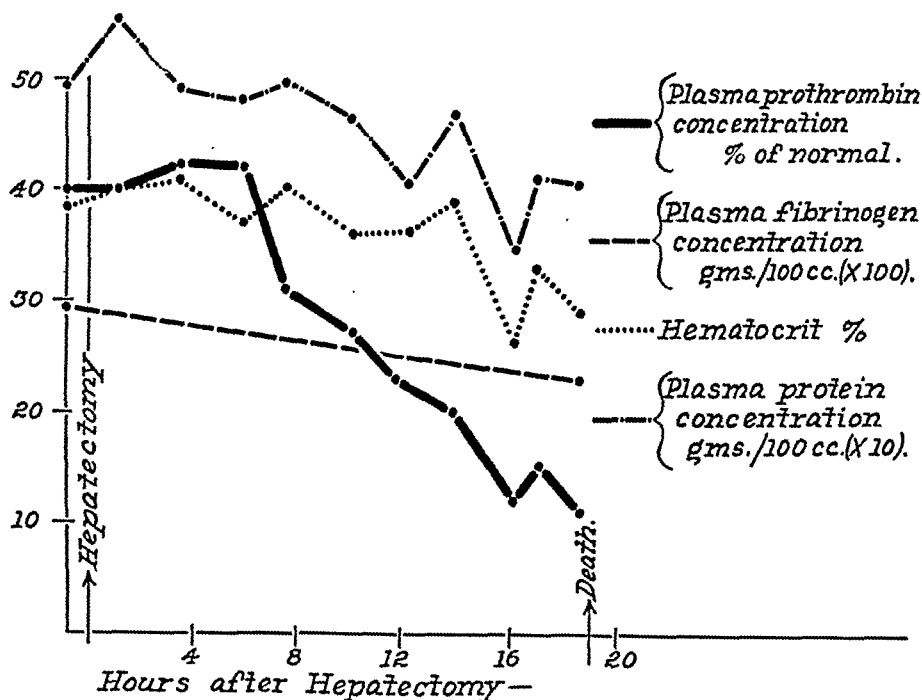


CHART 1.—Units for hematocrit, plasma-protein concentration, and plasma-fibrinogen concentration have been selected to demonstrate the relation of changes in these factors to changes in the concentration of plasma prothrombin.

Discussion. The data reveal irregular but definite declines in plasma-prothrombin concentration after total hepatectomy. The plasma-fibrinogen concentration also declined in a manner similar to that previously described by Jones and Smith⁶ and others. That this was not of such a degree as to affect the prothrombin determinations seriously was shown by the observation that excess fibrinogen added to the specimens did not decrease the prothrombin times as determined by the Quick⁸ method (Chart 3).

The consistently low plasma-prothrombin values in the dogs coming to the third stage of the multiple stage hepatectomy could be due to one or more of several factors which we plan to investigate.

We believe that the rapid decline in plasma-prothrombin concentration after hepatectomy is evidence that the site of prothrombin

synthesis has been removed. That it might be the result of a rapidly developing vitamin K deficiency due to the exclusion of bile from the intestinal tract is unlikely because Hawkins and Brinkhous⁵ found that 2 to 3 months were required for prothrombin deficiency to develop in dogs as the result of biliary fistula. Certainly the animals operated upon by the one-stage technique could have no deficiency of the vitamin K stores. This is demonstrated by the fact that dogs taken from our stock have undergone anastomosis of the gall bladder to the renal pelvis and subsequent diversion of all bile from the intestinal tract for as long as 15 weeks without

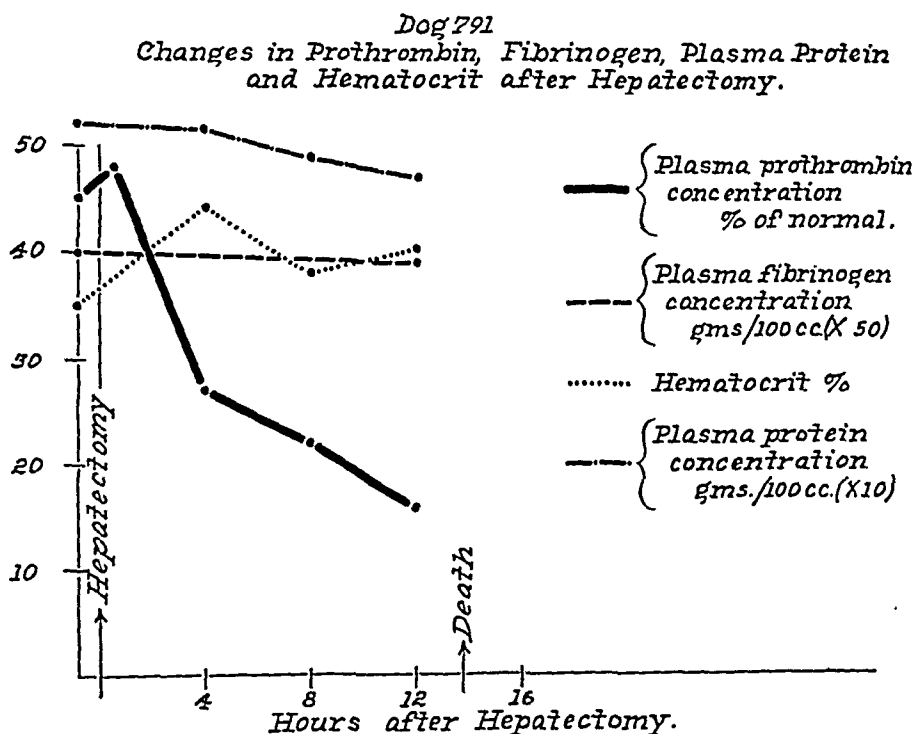


CHART 2.—Same units have been used for hematocrit, plasma-protein concentration and plasma-prothrombin concentration as in Chart 1; unit for plasma-fibrinogen concentration has been doubled.

the development of a prothrombin deficiency. Furthermore, dogs with recently established biliary fistulae have been able to regenerate prothrombin after a deficiency of this factor was produced by chloroform anesthesia.

In order to determine whether the drop in plasma-prothrombin concentration following hepatectomy might be produced by factors incidental to the operation a number of control animals were studied. It was found that hemorrhage, plasmapheresis, laparotomy for other procedures, and ether anesthesia for 3 hours, failed to produce plasma prothrombin deficiency in the normal stock dogs.

Conclusions. 1. A rapid decline in plasma-prothrombin concentration as determined by the method of Quick occurs in the dog after total hepatectomy.

2. A decline in fibrinogen concentration was also observed, but this was not sufficient to interfere with the prothrombin determinations.

Dog 691
Effect of Added Fibrinogen on Prothrombin Determinations.

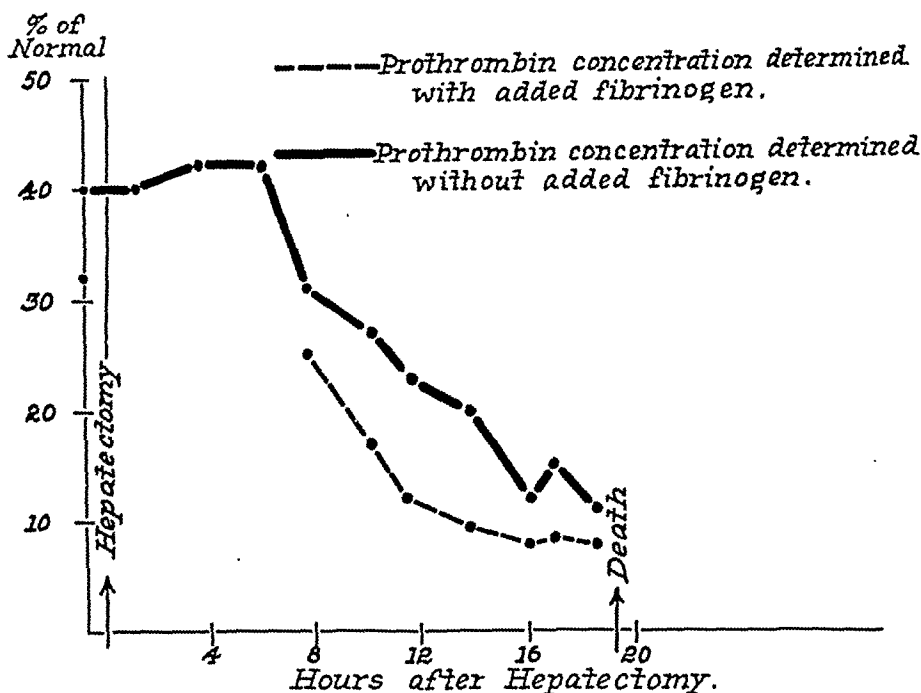


CHART 3.—Prothrombin concentration of the 2-hour, 4-hour and 6-hour specimens was not determined after the addition of fibrinogen.

3. The decline in plasma-prothrombin concentration could not be accounted for on the basis of anesthesia, hemorrhage, blood dilution, or laparotomy.

4. The liver is essential for the formation of prothrombin in the dog.

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THE EXPERIMENTAL PRODUCTION OF VITAMIN B₁ DEFICIENCY IN NORMAL SUBJECTS.

THE DEPENDENCE OF THE URINARY EXCRETION OF THIAMIN ON THE DIETARY INTAKE OF VITAMIN B₁*

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THE antineuritic vitamin has been known to be present in human urine since 1918,¹⁹ but quantitative estimation of the daily excretion of vitamin B₁ in the urine was not widely attempted until Birch and Harris⁴ developed the bradycardia method in 1934. Since then Harris and his co-workers,^{8,9} Roscoe,²³ and Baker and Wright^{2a} have used this method in estimating the excretion of vitamin B₁ in the urine. As this method requires the maintenance of a rat colony, and the estimation requires 7 to 10 days, its use was limited to experimental nutritional laboratories. Moreover, the reliability of the bradycardia method has been questioned. Keresztesy and Sampson¹⁵ have shown that vitamin B₁ depleted rats can utilize on the average only 60% of the vitamin adsorbed on the ingested acid clay. Robertson and Doyle²² have pointed out that the bradycardia method in their hands gave inconstant results. Knott¹⁶ has recently made balance studies on children, the food, urine and feces being assayed by a rat growth method.

Estimations of thiamin in the urine by chemical methods have been made in Jensen's laboratory^{27a,b,c} and elsewhere^{14,18,20,21,28} and by a fermentation method by Schultz and associates.^{17,25,26} These investigators, however, did not, to our knowledge, maintain their subjects with weighed diets of constant composition and of known vitamin B₁ content. Other workers^{1,6,13,24} gave to normal and hospital patients diets inadequate in vitamin B₁ but did not, to

* Preliminary report read before the fiftieth annual meeting of the American Physiological Society, April 1, 1938.

our knowledge, maintain their subjects with weighed diets of constant composition deficient only in vitamin B₁, nor did they determine daily the urinary excretion of vitamin B₁.

The recent development by Westenbrink and Goudsmit^{27a} of a fluorimetric method for the determination of thiamin (vitamin B₁) in the urine has made the study of its urinary excretion a practical procedure. We have used their method for the determination of thiamin with slight modifications, consisting essentially of substitution of permutit for acid clay as the adsorbant of thiamin from dilute acidulated urine, and visual comparison of the unknown with a series of thiochrome* standards in the fluorimeter† instead of the electrical measurement of fluorescence by photoelectric cell and string galvanometer.

The purpose of this study was twofold: (1) The experimental production of symptoms and signs of vitamin B₁ deficiency in normal subjects while maintained with a constant weighed diet of known vitamin B₁ content and of probable adequacy in all other dietary essentials; (2) the determination of the thiamin excretion in the urine of these subjects during control, deficiency and recovery periods.

Methods. The vitamin B₁ poor diet used in this study (Table 1) is probably adequate for normal man except in vitamin B₁. The vitamin B₁/calory ratio was calculated from Cowgill's tables⁵ to give a value of 1.

TABLE 1.—VITAMIN B₁ POOR DIET.

Article.	Grams or cc.	Article.	Grams or cc.
Lean beef*	100	Polished rice	50
Beets†	250	Honey	50
American cheese	100	Glucose	60
Apple or banana	200	Butter	100
White bread	150	Ginger ale	500
Macaroni	50	Candy	25
0.1 N hydrochloric acid	6	Liver fraction‡	15
Halibut liver oil	0.2	Ferrous sulphate	0.2
Cevitic acid	0.05		

Estimated from Cowgill's tables to contain approximately carbohydrate, 380 gm., protein, 80 gm., fat, 140 gm., calories, 3150, vitamin B₁, 3150 mg. eq. of Cowgill (158 International Units or 0.474 mg. of thiamin) and a vitamin B₁/calory ratio of 1. Estimated from tables of Williams and Spies²⁹ to contain 0.360 mg. of thiamin, giving a thiamin/calory ratio of 0.11 and a thiamin/non-fat calory ratio of 0.2.

* Lamb or chicken could be substituted without significant change in vitamin B₁ or calories.

† Carrots, onions, cauliflower, egg plant, kohlrabi, green peppers, spinach, young string beans, tomatoes can be substituted without a significant change in vitamin B₁ and with but little change in total calories.

‡ Derived from 480 gm. of liver and free of vitamin B₁. By courtesy of Dr. Guy Clark, Lederle Laboratories, Pearl River, N. Y.

This ratio supplies 50% of Cowgill's predicted minimum vitamin B₁ requirement for a subject weighing 70 kg. The 100 gm. of butter in this diet was given a value of 800 mg. equivalent of vitamin B₁, which accounts for about 25% of the estimated vitamin B₁ content of this diet. We are

* Courtesy of Merck & Co., Rahway, N. J.

† Made by Hanovia Chemical and Manufacturing Co., New York City.

aware that this figure may not represent thiamin as such but the vitamin B₁ sparing properties of butter fat. The thiamin content as estimated from the tables of Williams and Spies²⁹ is 0.360 mg. giving a thiamin/calory ratio of 0.11 and a thiamin/non-fat calory ratio of 0.2.

Supplements of ferrous sulphate, cevitic acid, halibut liver oil and a liver fraction were included in the diet to insure its adequacy in iron, vitamins A, B₂-complex, C and D. The supplement of hydrochloric acid, 3 cc. of which was given to each subject throughout the experiment, at the noon and evening meal, was included as a vehicle for the thiamin* which was added during the control and recovery periods only. By this method we hoped that the subjects would not be aware of the addition or withdrawal of thiamin. The diet was divided into 3 meals daily, except for the ginger ale, which was usually taken at night before retiring. The diet was accurately weighed and prepared by the Division's chief dietitian, Miss Bertha Weiss; it was consumed by all 5 subjects in its entirety at all times. They were not permitted any other source of calories. As large amounts of both natural and synthetic thiamin were available, we believed the experimental production of vitamin B₁ deficiency to a degree sufficient to produce early objective signs was not likely to be followed by permanent or irreversible damage. We thought it advisable, however, before using normal lay volunteers to demonstrate the safety of this procedure in subjects fully cognizant of the possible dangers. Consequently, the subjects of this study consisted of 2 of us (R. G. and J. G.) and 3 resident physicians. All subjects continued at their hospital duties during the term of the experiment.

The experimental observations on each subject were divided into three periods: control, deficiency and recovery. During the control period two subjects (R. G. and M. H.) received a weighed diet estimated to contain 2875 calories and 16.225 mg. equivalent (811 international units, 2.43 mg. as thiamin) of vitamin B₁. This diet supplied a vitamin B₁/calory ratio of 5.64 which is 2.75 and 2.68 times the minimum vitamin B₁ requirement⁵ of these 2 subjects respectively. One subject (M. H.) complained so bitterly of hunger during the control period that on the ninth day each item of the diet was increased by 50%. The vitamin B₁/calory ratio was thus maintained constant. The other 3 subjects (M. T., A. M., and J. G.) during the control period were given the vitamin B₁ poor diet plus 2.16 mg. of synthetic thiamin. This gives a vitamin B₁/calory ratio of 5.64 which is 2.45, 2.89, and 3.52 times the minimum predicted vitamin B₁ requirement of these three subjects respectively. During the deficiency period all subjects received only the vitamin B₁ poor diet. In the recovery period, all subjects continued with the vitamin B₁ poor diet, and thiamin was added to the hydrochloric acid supplement in amounts designated on the chart of each subject.

The observations reported here were made at daily or frequent intervals throughout the control, deficiency and recovery periods. They include subjective symptoms, detailed physical examination, electrocardiographic tracings by the 3 standard leads, and estimation of the thiamin excretion on 10 cc. portions of accurate 24-hour urine samples collected under toluene, acidified, and kept in a refrigerator. Other observations not reported at this time include basal metabolism determinations, blood chemistry including vitamin B₁, hematologic studies and teleoroentgenograms at frequent intervals.

Results. Detailed data for each of the 5 subjects are given in Figures 1 to 6. They will be presented under 3 headings: the

* Courtesy of Merck & Co., Rahway, N. J.

early symptoms of vitamin B₁ deficiency; the early objective signs of vitamin B₁ deficiency; and the relation of the dietary intake of vitamin B₁ to the excretion of thiamin in the urine.

VITAMIN B₁ EXCRETION IN URINE

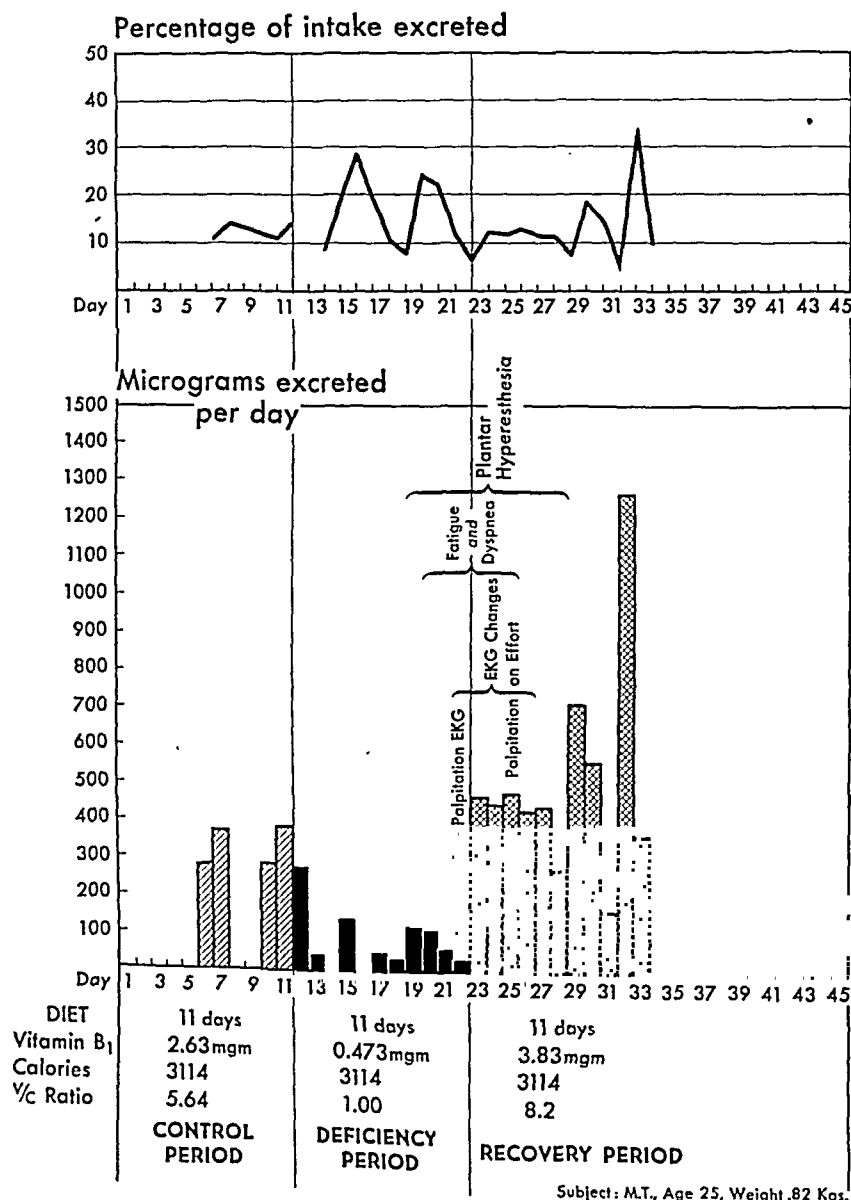


FIG. 1.—Data on Subject M. T.

The Early Symptoms of Vitamin B₁ Deficiency.—During the control period the subjects offered no complaints except that the 3 (M. T., J. G., and A. M.) who were maintained with the vitamin B₁

poor diet plus 2.16 mg. of thiamin daily all complained of constipation for the first 2 or 3 days. This condition was relieved spontaneously. The appetites of all subjects were maintained.

VITAMIN B₁ EXCRETION IN URINE

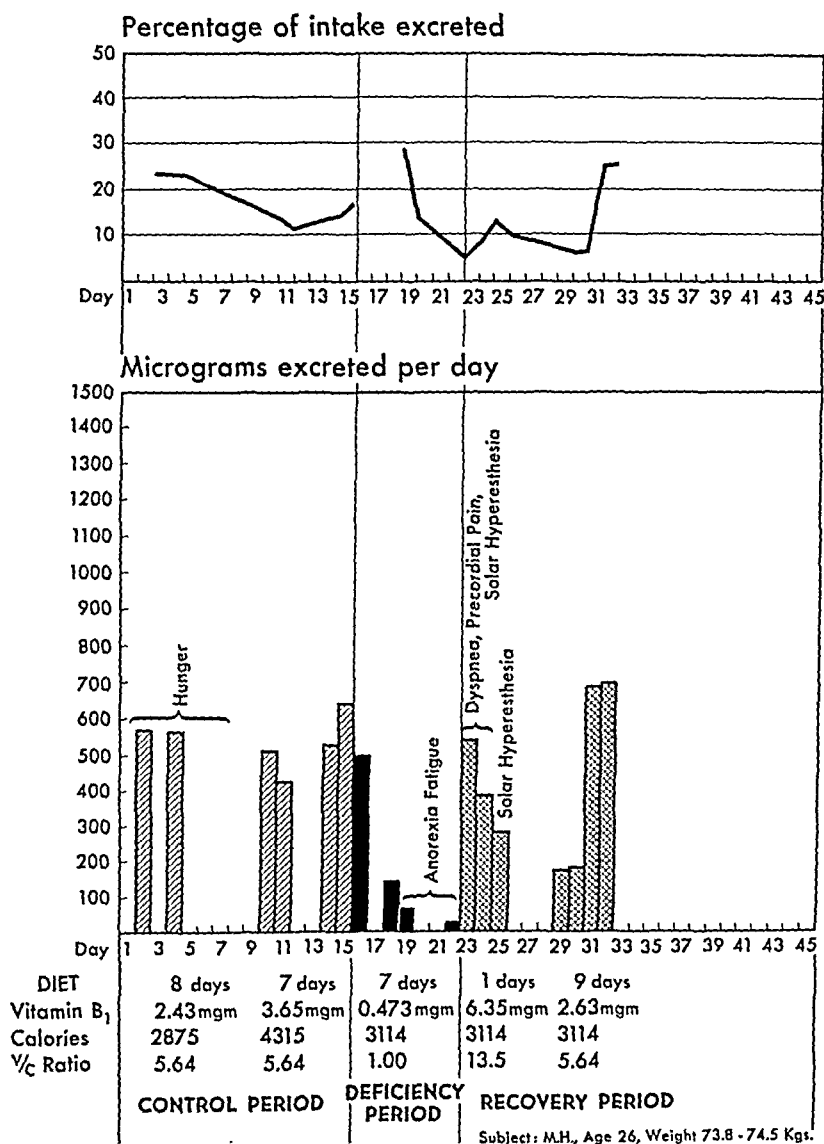


FIG. 2.—Data on Subject M. H.

Deficiency of vitamin B₁ was initiated by placing R. G. and M. H. on the vitamin B₁ poor diet, and by withdrawing the 2.16 mg. of thiamin from the hydrochloric acid supplement in the vitamin B₁

poor diet of M. T., J. G. and A. M. The first few days of the deficiency period were symptom free. On the 3d or 4th day the subjects began to complain of the monotony of the diet. All sub-

VITAMIN B, EXCRETION IN URINE

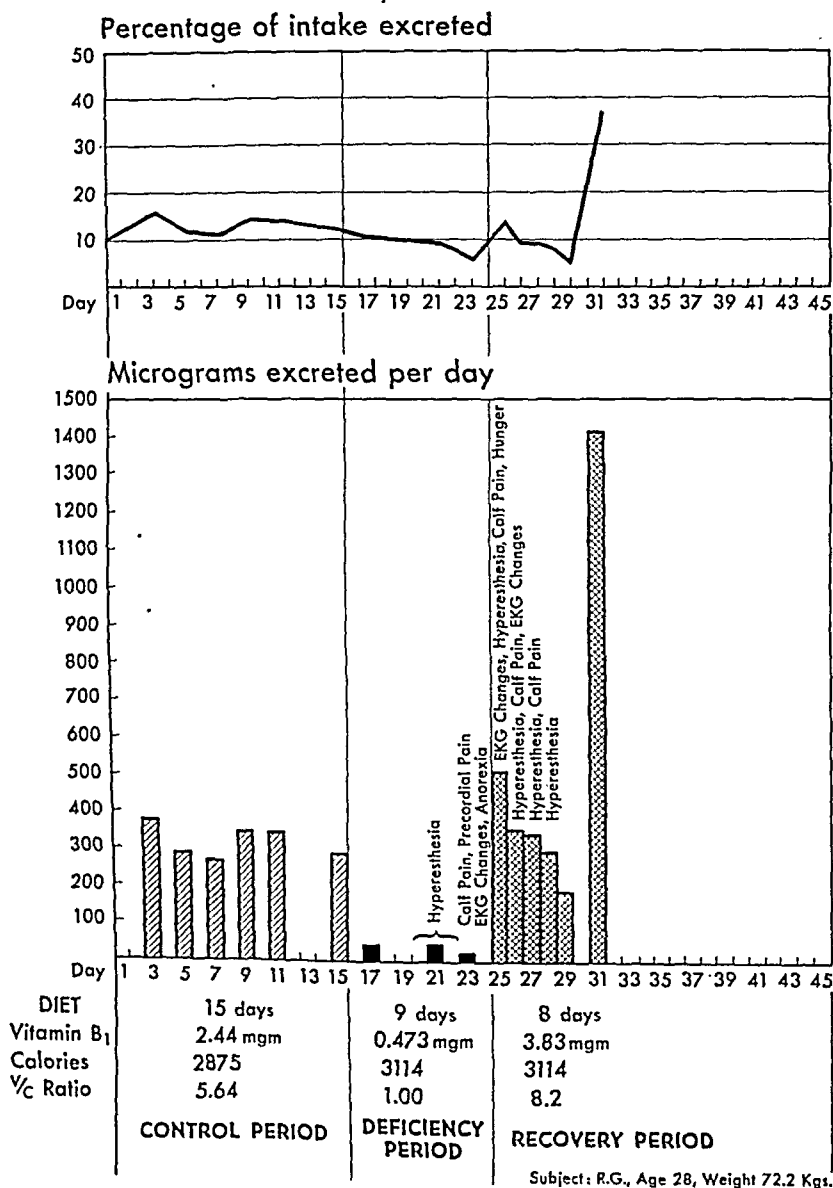


FIG. 3.—Data on Subject R. G.

jects developed symptoms, in 4 of whom they seemed definite. The symptom common to all 5 subjects was fatigue. It occurred as early as the 4th day of the deficiency period in M. H., the 8th

day in R. G., the 9th day in M. T., the 11th day in A. M., and by the 13th day in J. G. In the latter subject, this complaint disappeared spontaneously by the 18th day and did not reappear even

VITAMIN B₁ EXCRETION IN URINE

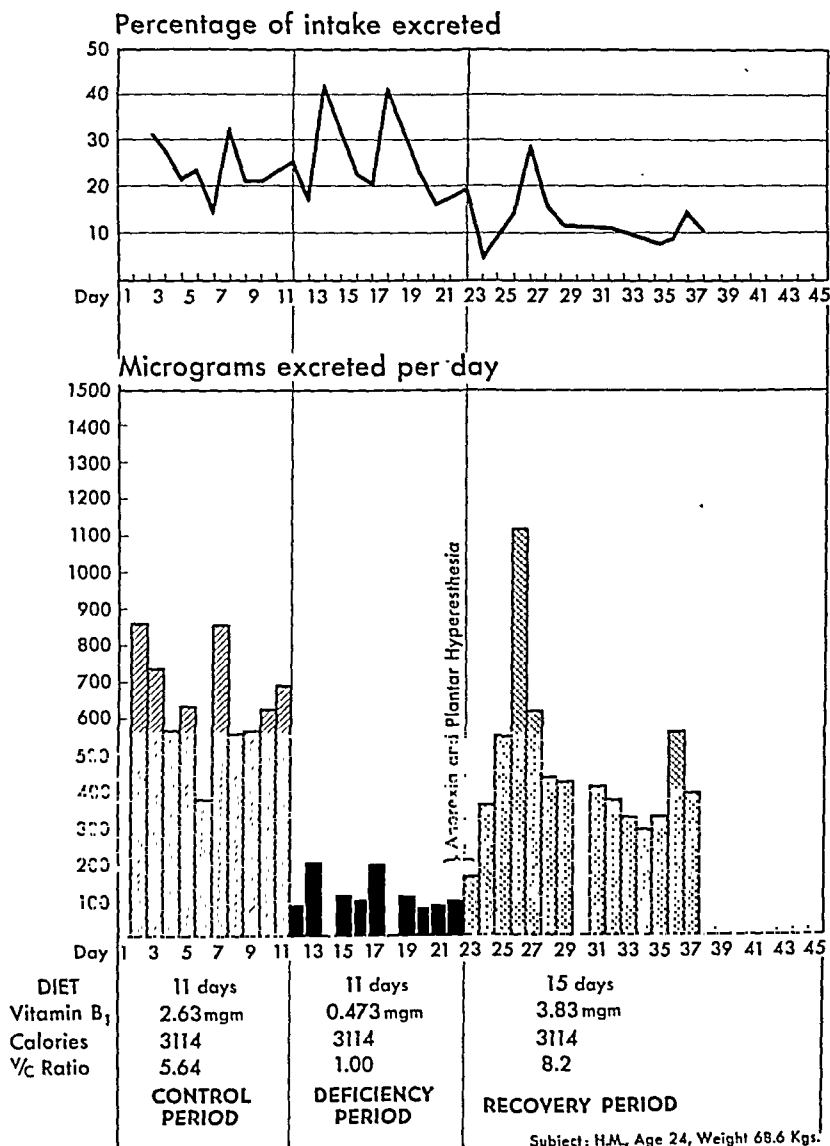


FIG. 4.—Data on Subject A. M.

though the deficient diet was continued for an additional 12 days. Four subjects complained of anorexia. It occurred as early as the 4th day in M. H., the 8th day in R. G., the 9th day in M. T., and

the 11th day in A. M. The anorexia seemed definite and it was only by considerable will-power that these 4 subjects consumed the diet in its entirety. Symptoms referable to the cardiovascular

VITAMIN B, EXCRETION IN URINE

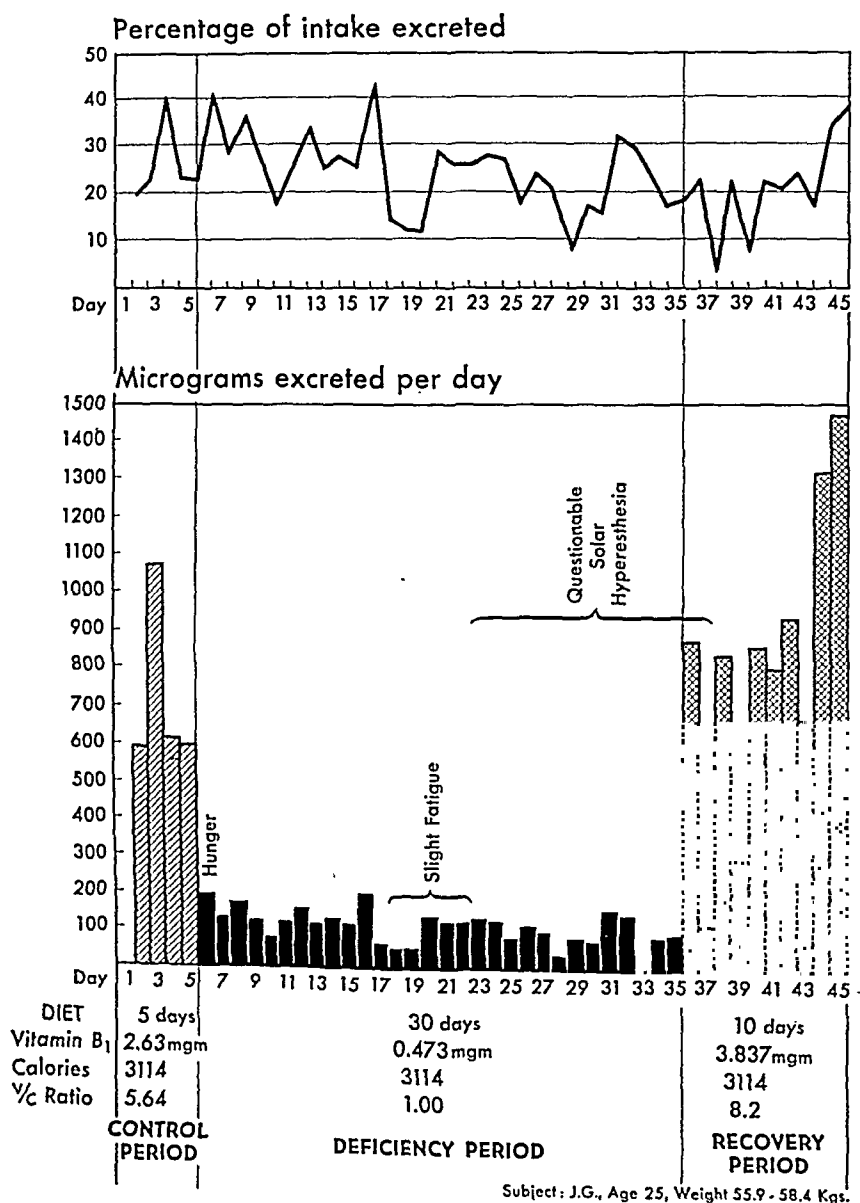


FIG. 5.—Data on Subject J. G.

system occurred in 3 subjects (M. H., M. T., R. G.). The symptoms were dyspnea on slight exertion in 2 subjects (by the 8th day in M. H., and by the 9th day in M. T.) and precordial pain in

3 subjects (by the fifth day in R. G., by the 8th day in M. T., and by the 11th day in M. H.), and palpitation in 1 subject (M. T. on the 12th day). These symptoms, though subjective, seemed definite. The precordial pain occurred on effort, lasted for 2 to 3 hours, was aching in character, precordial and substernal in location, and did not radiate to the shoulders, neck or arms. The dyspnea and fatigue in M. H. was so severe that he was unable on the 8th day of his deficiency period (1st day of recovery period) to walk up a flight of stairs without resting or to continue his duties as house physician.

Neurologic symptoms were observed in 3 subjects, all of whom complained of burning of the feet, especially at night. This symptom was first noted on the 5th day by R. G. and on the 8th day by M. H., and M. T. Cramps in the calf and feet muscles occurred in 2 subjects (M. H. and R. G.) by the 7th and 8th days respectively. Paresthesias were not noted by any subject.

The addition of thiamin to the vitamin B₁ poor diet, which marked the beginning of the recovery period, was followed by the prompt disappearance of all symptoms, in that no subject had any abnormal complaints after the 3d day of the recovery period. By this time anorexia had given way to hunger. The fatigue and lassitude which had been obvious to all who observed these subjects, was replaced by a feeling of well-being; burning of the feet, muscle cramps, precordial pain, dyspnea and palpitation were no longer present. The relief of symptoms occurred without the subjects being aware, except from the change in their own subjective feelings, that thiamin had been added to the hydrochloric acid supplement. The amount of thiamin added to the vitamin B₁ poor diet was 3.36 mg. daily except in the diet of M. H. This subject, whom we had to put to bed because of extreme fatigue and exhaustion, and who gave us considerable concern, received on the first recovery day 5.877 mg. of thiamin, which we calculated to be his accumulated deficit during the 7 days of his deficiency. For the remainder of his recovery period he was given 2.16 mg. of thiamin daily.

The Early Objective Signs of Vitamin B₁ Deficiency.—Objective signs of vitamin B₁ deficiency occurred in 4 subjects and were limited to hyperesthesia, calf tenderness, and changes in the electrocardiogram. Definite hyperesthesia was limited to the plantar surface of the feet in all these subjects except M. T., in whom by the 12th day (1st day of recovery period) it extended to the mid-calf of both legs in a sock distribution. The hyperesthesia to pin prick or scratch was not associated with changes in temperature, tactile, two-point discrimination, position sense, or vibratory sensation. Calf muscle tenderness was elicited in only 1 subject (by the 8th day in R. G.). Changes in the electrocardiographic tracings were noted in 2 subjects. In R. G. (Fig. 6) the changes

SUBJECT R. G.

Control Period

Lead I



Lead II



Lead III



Deficiency Period

Lead I



Lead II



Lead III



Recovery Period

Lead I



Lead II



Lead III



FIGURE 6.

SUBJECT M. T.

Control Period

Lead I



Lead II

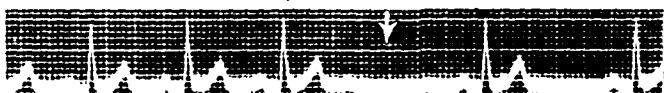


Lead III



Deficiency Period

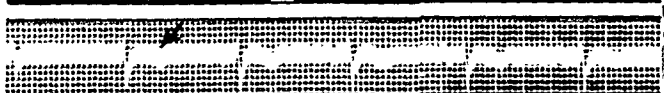
Lead I



Lead II



Lead III



Recovery Period

Lead I



Lead II



Lead III

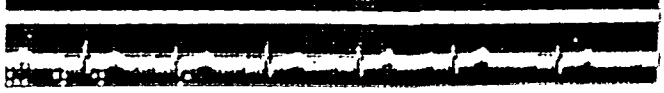


FIGURE 7.

occurred by the 8th day of the deficiency period and consisted of inversion of T₃. In M. T. (Fig. 7) electrocardiographic changes occurred by the 11th day of the deficiency period and consisted of sinus arrhythmia, sinus arrest, change in deviation of the electrical axis, and inversion of T₃. J. G., the smallest of the subjects, developed no definite objective sign of vitamin B₁ deficiency.

None of the following objective signs was noted: nystagmus, ataxia, changes in tendon reflexes, changes in the oral mucous membranes, dilated neck veins, epigastric pulsations, changes in size or shape of the heart, development of heart murmurs, changes in heart sounds, palpable liver, or peripheral edema.

When thiamin was added in the recovery period, the objective signs disappeared in the reverse order of their occurrence. Plantar hyperesthesia was the first to develop and was the last to disappear. It remained for 6 days in M. T., 4 days in R. G., 3 days in M. H., and 2 days in A. M. The electrocardiographic changes disappeared by the 3d recovery day in R. G. and by the 5th recovery day in M. T.

The Relation of the Dietary Intake of Vitamin B₁ to the Excretion of Thiamin in the Urine.—Inspection of the figures on the individual subjects (Figs. 1 to 5) immediately discloses that the urinary excretion of thiamin is roughly proportional to the dietary intake of vitamin B₁. It is also evident that the urinary excretion reflects, as a rule within 24 hours and always within 48 hours, changes in vitamin B₁ intake of the magnitude used in this study. This is true whether vitamin B₁ is added or removed from the diet.

In addition, it can be noted that during the deficiency period subjective symptoms did not occur unless the excretion of thiamin fell below 100 micrograms daily, and in 1 subject (R. G.) subjective symptoms did not occur until a level of about 30 micrograms was reached. The 3 subjects complaining of precordial pain and the 2 subjects showing electrocardiographic changes did not develop these symptoms or signs until the urinary excretion had fallen below 30 micrograms. During the recovery period, the symptoms and signs noted above did not promptly disappear when the urinary excretion of thiamin exceeded 100 micrograms daily.

The average thiamin excretion during the control period varied from 319 micrograms (R. G.) to 676 micrograms (J. G.), accounting for 13.1 to 25.7% of the estimated intake. During the deficiency period, omitting the first 3 days of this period as reflecting to some extent the intake during the control period, the average thiamin excretion varied from 35 micrograms (R. G.) to 108 micrograms (J. G.), accounting for 7.4 to 23% of the estimated intake. In the recovery period, the average thiamin excretion varied from 339 micrograms (R. G.) to 806 micrograms (J. G.), accounting for 11.7 to 21.1% of the estimated intake.

A considerable variation exists, it is evident, in the relative and absolute amounts of thiamin excreted. There is some indication (Table 2) that the smaller subjects (A. M. and J. G.) excreted more thiamin than the larger subjects (M. T., M. H., and R. G.) when maintained with the same vitamin B₁ intake. We have therefore studied the relation between the excretion of thiamin and the adequacy of the vitamin B₁ intake as judged by Cowgill's prediction formula⁵ by a correlation of the thiamin excretion in micrograms with the ratio of vitamin B₁ intake/predicted minimum requirement (hereafter called the intake/requirement ratio). An intake/requirement ratio of 1 represents just a maintenance intake of vitamin B₁ and takes into consideration the individual's size and caloric intake. Such a correlation would naturally present considerable spread due not only to individual variations of an undetermined nature but also to a difference in the total metabolism of the individual subjects. When the intake/requirement ratio is between 2.5 and 5 there is excreted in our subjects at least 300 micrograms of thiamin daily. In this range, 1 subject averaged 800 micrograms daily. On the other hand, when the ratio was 0.4 to 0.65 the average excretion of thiamin was 110 micrograms or less daily. Insufficient data are at hand at the present time to judge whether these figures represent even a first approximation of the range of excretion of thiamin under the conditions of this study.

TABLE 2.—DATA ON INDIVIDUAL SUBJECTS BY AVERAGES OF PERIODS.

Subject.	Wt., kg.	Predicted minimum requirement as Vit. B ₁ /cal.	Period.	Vitamin B ₁ intake as:		Ratio.	Average excretion of thiamin, mg.	Mg.	% of intake.
				Mg. thiamin.	Vit. B ₁ /cal.				
						Intake P.M.R.*	No. of deter- minations.		
M. T.	82	2.30	Control	2.633	5.64	2.45	8	0.377	14.3
			Deficiency	0.473	1.0	0.43	7	0.073	15.4
			Recovery	3.837	8.11	3.52	11	0.390	10.2
M. H.	74.5	2.10	Control 1	2.436	5.64	2.68	2	0.565	23.1
			Control 2	3.654	5.64	2.68	4	0.525	14.4
			Deficiency	0.473	1.0	0.47	2	0.044	9.3
			Recovery	2.633	7.65	3.64	6	0.394	15.0
R. G.	72	2.05	Control	2.436	5.64	2.75	6	0.319	13.1
			Deficiency	0.473	1.0	0.47	2	0.035	7.4
			Recovery	3.833	8.11	3.95	5	0.339	11.7
A. M.	68.5	1.95	Control	2.633	5.64	2.89	10	0.644	24.4
			Deficiency	0.473	1.0	0.51	7	0.110	23.2
			Recovery	3.833	8.11	4.15	14	0.447	11.7
J. G.	56	1.60	Control	2.633	5.64	3.52	5	0.676	25.7
			Deficiency	0.473	1.0	0.62	26	0.108	23.0
			Recovery	3.833	8.11	5.07	10	0.806	21.1

* P.M.R. = Predicted minimum requirement.

Comment.—The rapid production of both symptoms and objective signs of vitamin B₁ deficiency was in the beginning an unexpected result. Jolliffe, Colbert and Joffe¹² have estimated that "an individual may develop polyneuritis if the caloric need is satisfied by a diet free of vitamin B₁ for a period of a week, while every individual in our series had polyneuritis if the period of 'estimated absolute deficiency' was 21 days or more." The days of "estimated absolute deficiency" was calculated by multiplying the per cent of deficiency, as estimated from Cowgill's predicted minimum requirement, by the number of days over which the deficiency occurred. On this basis, our subjects accumulated the following number of days of "estimated absolute deficiency" before subjective symptoms developed: A. M. 5.4 days, M. T. 5.1 days, R. G. 4.2 days, M. H. 2.1 days. Objective signs were first observed after the following days of "estimated absolute deficiency": A. M. 5.4 days, M. T. 4.5 days, R. G. 4.2 days and M. H. 4.2 days. On the other hand, J. G. accumulated 11.4 days of estimated absolute deficiency without development of either subjective symptoms or objective signs.

In the previous study,¹² the calculated days of "estimated absolute deficiency" represented the minimum period over which the deficiency existed that produced definite signs of peripheral neuritis sufficient to fulfill the criteria for the diagnosis of polyneuritis as defined by Goodhart and Jolliffe.⁷ In this study, the accumulated days of "estimated absolute deficiency" is considerably less than in the previous study. In the subjects of this study, a diagnosis of peripheral neuritis due to vitamin B₁ deficiency would not have been made by Jolliffe, Colbert and Joffe,¹² as the signs were not sufficient to fulfill the criteria for the diagnosis of polyneuritis as defined by Goodhart and Jolliffe.⁷ On the other hand, the signs and symptoms developed with the vitamin B₁ poor diet and were relieved with the addition of synthetic thiamin alone; we therefore believe they can be attributed only to the lack of vitamin B₁.

That signs and symptoms may develop as rapidly as seen in this study with diets only moderately restricted (43 to 62% adequate) has many clinical implications. It suggests the possibility of a high prevalence of mild vitamin B₁ deficiency in the general population, which thesis has recently been elaborated by Jolliffe;¹¹ that vague ill-health characterized particularly by fatigue and persistent anorexia may be a manifestation of suboptimal intake of vitamin B₁; that when patients are treated with oral, parenteral or rectal feedings of dextrose or other vitamin free sources of calories, proper attention should be given to the vitamin B₁ supply, even though such a regimen extends over but a few days; that some of the errors in the diagnosis of coronary artery disease recently pointed out by Herrick¹⁰ and Bean³ may be eliminated by critical

evaluation of the diet, and that if the diet is found borderline or inadequate, or if the subject has other clinical signs of vitamin B₁ deficiency, a therapeutic trial should be instituted.

Harris, Leong and Ungley⁹ have stated that when a steady state has been reached the excretion of vitamin B₁ "remains fairly constant at around 5 to 8 per cent of the intake, notwithstanding the wide variation in the latter." The excretion of thiamin as reported by these observers is lower than the results found in this study. Recalculation of certain of their results on the basis of an average recovery¹⁵ by the rat of 60% of the ingested vitamin adsorbed on acid clay and of 1 international unit of vitamin B₁ being equivalent to 3.3 micrograms of thiamin, makes our results more comparable with theirs. For example, 7 of their "Normal Controls, Cambridge and London, May-October, 1935,"⁹ not supplementing their diet by wheat germ, excreted 66 to 126 micrograms of thiamin daily. On the basis that their subjects had an average daily intake of 250 international units (825 micrograms of thiamin), which Harris and Leong⁸ and Baker and Wright²⁶ have estimated as the average vitamin B₁ intake of middle class Englishmen, the daily excretion varied from 8 to 15.3% of the intake. On the basis of the same intake, the 8 "Normal Controls, Cambridge and London, February-March, 1937,"⁹ not supplementing their diet with wheat germ, excreted from 10 to 22% of their intake. To a single subject whose diet they⁸ estimate as averaging 250 international units of vitamin B₁, they gave an additional 110 to 1000 international units of vitamin B₁. Recalculation of these data indicates an excretion of 6 to 13% of the ingested vitamin B₁. Thus Harris' subjects excrete from 6 to 22% of their ingested vitamin B₁, while our subjects excrete from 7 to 25%. There is, therefore, not much difference in the range of excretion of thiamin as reported by us in this paper and the range reported by Harris and co-workers as recalculated by us. Most of our values, however, are in the upper levels and most of Harris' in the lower levels of this range of values. This apparent difference may be due not only to the difference in methods but to the difference in size of the subjects in the two studies and to the fact that our subjects consumed a constant weighed diet, while their subjects consumed an *ad lib.* diet the value of which was taken as "average."

Summary and Conclusions. We have experimentally produced in 4 of 5 normal human volunteers the signs and symptoms of early vitamin B₁ deficiency and studied in all the relation of the dietary intake of vitamin B₁ to the urinary excretion of thiamin. These subjects were maintained with accurately weighed diets of known content of vitamin B₁ and presumably adequate in all other essential elements of nutrition.

Definite symptoms and signs were observed in 4 of the 5 subjects while they were maintained with a vitamin B₁ poor diet. Symptoms were observed as early as the 4th day and objective signs as early as the 5th day, though 1 subject developed no definite symptom or objective sign in 30 days with a diet estimated to contain 62% of his predicted minimum vitamin B₁ requirement. The symptoms observed were fatigue and lassitude, anorexia, precordial pain, burning of the feet, dyspnea on exertion, muscle cramps and palpitation. The objective signs observed were skin hyperesthesia in a sock distribution, changes in the electrocardiogram, and calf muscle tenderness. The addition of thiamin alone to the vitamin B₁ poor diet caused all symptoms to disappear within 3 days and the objective signs within 6 days.

Our subjects excreted in the urine as thiamin 7 to 25% of the ingested vitamin B₁ (averaged periods). There was, under the conditions of this study, a good correlation in each subject between the vitamin B₁ intake and the urinary excretion of thiamin. Changes in the vitamin B₁ intake are early reflected by changes in the excretion of thiamin. With the same vitamin B₁ intake the excretion level varies from subject to subject but is roughly proportional to the adequacy of the diet as expressed by the ratio of vitamin B₁ intake/predicted minimum requirement.

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**THE RELATION OF THE ADRENAL GLANDS TO THE
ACTION OF THE RENAL PRESSOR SUBSTANCE.***

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PREVIOUS work^{1,7} has shown that renal cortical tissue contains a substance (called "renin" by Tigerstedt and Bergmann⁸) which causes a well marked rise in blood pressure when administered intravenously to animals. Whether this substance plays any rôle in the control of vascular tone in the kidneys or elsewhere in health or disease is not definitely known. In view of its possible endocrine nature a study has been undertaken of the relationship of some of the endocrine organs to renin.

Methods. Rats were used. In one series of experiments various endocrine organs—either the adrenal glands, the hypophysis or the gonads—were removed. Several days later the sensitivity of these animals to a standardized extract of hog kidney was compared with that of normal rat. Sodium pentobarbital was administered intraperitoneally in doses of 4 mg. per 100 gm. of body weight, the lower abdominal aorta was cannulated, and the blood pressure was measured before and after the administration of the renal extract. Prior to the insertion of the aortic cannula the kidneys of the animals were removed and used for the preparation of renin. Subsequently the pressor effect of extracts prepared from the kidneys of the normal and treated animals was compared.

In another series of experiments, animals previously prepared by the injection of various sex hormones were similarly compared with controls as regards sensitivity to hog renin and as regards the renin content of their kidneys.

The technique used for the preparation of renin was that described by Grossman.⁴

Throughout the experiments care was taken that the controls and the treated animals should be approximately the same age and size, for Grossman and Williams⁵ have shown that rats of different ages display marked variations in their response to the renal pressor substance.

Results. Since the most striking results were those obtained in adrenalectomized rats, these will be considered first.

Observations on Adrenalectomized Rats. In 7 different experiments a group of normal animals was compared with a group of rats which had been subjected to adrenalectomy 2 to 10 days previously, and subsequently treated with daily injections of 10 cc. of 0.9% sodium chloride solution. Each group consisted of from 2 to 5 animals.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation.

In each instance the initial blood pressure of the adrenalectomized rats was lower than that of the controls, the difference varying from a few millimeters to 55 mm. In 6 of the 7 experiments the adrenalectomized animals displayed marked diminution in sensitivity to the renal extract as compared with the controls (Figure 1). In the

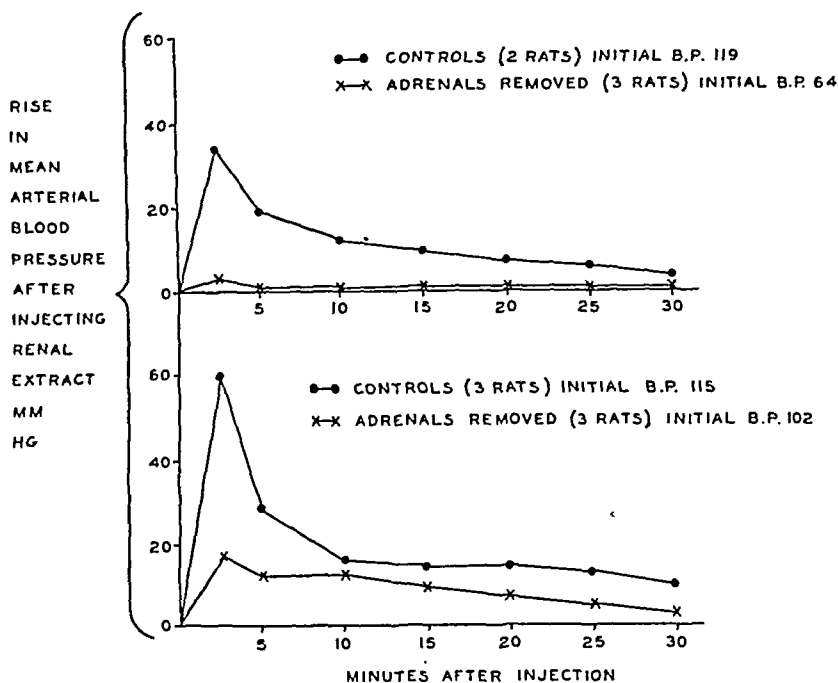


FIG. 1.—Effect of adrenalectomy on the response to the renal pressor substance. These are examples of a day's experiment. It is seen that the rats whose adrenals have been removed are very much less sensitive to renin than are the control rats. In the lower chart, the average initial blood pressure of the adrenalectomized rats is only slightly less than the normals; in the upper, it is 55 mm. less. The results are essentially the same, the renin being less active after adrenalectomy regardless of the initial blood pressure.

seventh experiment, the two groups of animals were about equally sensitive.

The findings seem at first sight to be contrary to those of Merrill, Williams and Harrison,⁶ who found that removal of the adrenal glands immediately before the injection of renin did not alter the response. Accordingly, comparisons were made in the present study between rats subjected to adrenalectomy several days previously, rats from whom the glands were removed immediately prior to the injection of renin, and control animals. As shown in Figure 2, consistent differences between the two latter groups were not encountered. However, both of these groups responded to renin with a much greater rise in blood pressure than did the animals which had been deprived of adrenal tissue for several days.

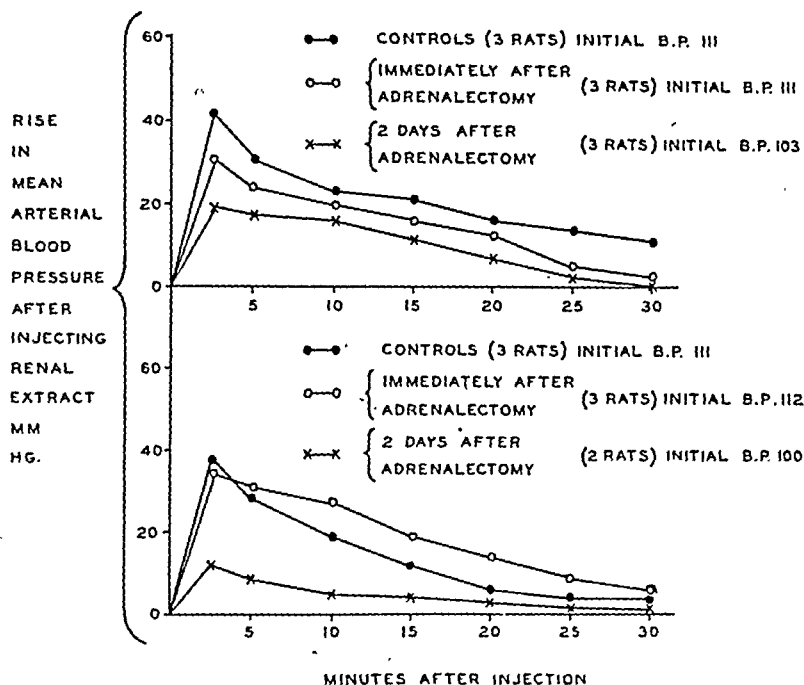


FIG. 2.—Change in response to renin immediately, and 2 days after removal of the adrenal glands. In one group of experiments, immediately after removal of the adrenals, the rats are slightly more sensitive to the renal pressor substance; in the other, slightly less. Two days after adrenalectomy the rats are definitely less sensitive.

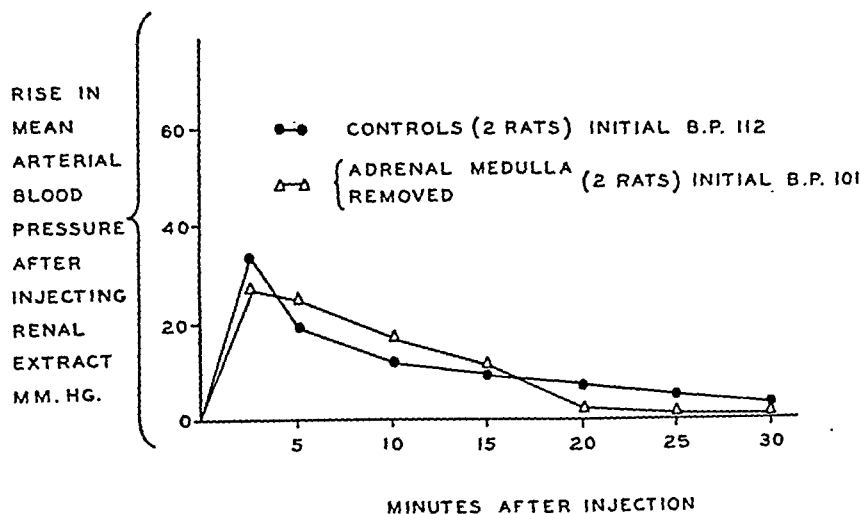


FIG. 3.—Effect of removing the adrenal medulla on the response to renin. This shows that in rats whose adrenal medullas have been removed there is no change in sensitivity to renin.

Removal of the adrenal medulla did not alter significantly the response of rats to renin (Fig. 3).^{*} It is apparently the adrenal cortex which is important in this regard. It might be argued that our adrenalectomized rats failed to respond to renin because such hypotensive animals were in poor general condition and would be unresponsive to any stimulus. The following facts indicate that such was not the case: 1, Some of the adrenalectomized rats had blood pressures only slightly lower than the controls and yet displayed marked diminution in sensitivity when renin was injected. 2, Hypophysectomized animals which had blood pressures as low as the adrenalectomized rats displayed a greater response than normal to the renal pressor substance. 3, In 13 adrenalectomized rats which were hyposensitive to renin, the blood pressure response to adrenalin was somewhat greater than that in the control animals. It therefore appears that the diminished sensitivity of adrenalectomized rats to the renal pressor substance is not simply due to poor general condition but represents a specific response as the result of the absence from the body of some substance formed in the adrenal cortex.

Twenty-eight comparisons between the renin content of the kidneys of normal rats and of the adrenalectomized rats were made by injecting extracts of these kidneys into normal rats. In 15 instances a greater rise in blood pressure was obtained from the extracts of the kidneys of the adrenalectomized animals. The reverse result was encountered once. Twelve comparisons gave inconclusive results.[†]

The observations which have been cited indicate definitely that the adrenalectomized rat is less sensitive than normal to the renal pressor substance, and that this difference is due to the absence from the body of something formed in the adrenal cortex rather than to the absence of the glands themselves. However, the kidneys of adrenalectomized rats are not deficient in the renal pressor substance.

Observations on Hypophysectomized Rats. Four groups of hypophysectomized animals were compared with normal animals of the same size and of approximately the same age, according to the technique described above, the observations being made 14 to 18 days after hypophysectomy (each group consisted of 2 to 5 rats). In one series of animals no difference was noted between the responses to renin of the treated rats and the controls. Postmortem examination revealed that hypophysectomy was incomplete in each of these

^{*} We are indebted to Dr. Arthur Grollman, who kindly supplied us with several rats from which the adrenal medulla had been removed some weeks previously.

[†] We arbitrarily consider differences of less than 5 mm. as inconclusive. Apparently the kidneys of adrenalectomized animals are somewhat richer in the renal pressor substance. We do not regard this point as definitely established, however, because in preparing the extracts allowance was not made for the dehydrated condition of the kidneys of the treated animals.

animals. Three groups of animals in which hypophysectomy was found to be complete showed a markedly lower (35 to 63 mm.) average blood pressure than did the controls. In each of these instances the treated animals displayed a slightly greater initial rise in blood pressure and a considerably greater sustained elevation after injection of the renal pressor substance than did the controls (Fig. 4 A). Whether this difference was specifically dependent on the absence of hypophyseal tissue or was due to the lower initial blood pressure of the treated animals is uncertain.

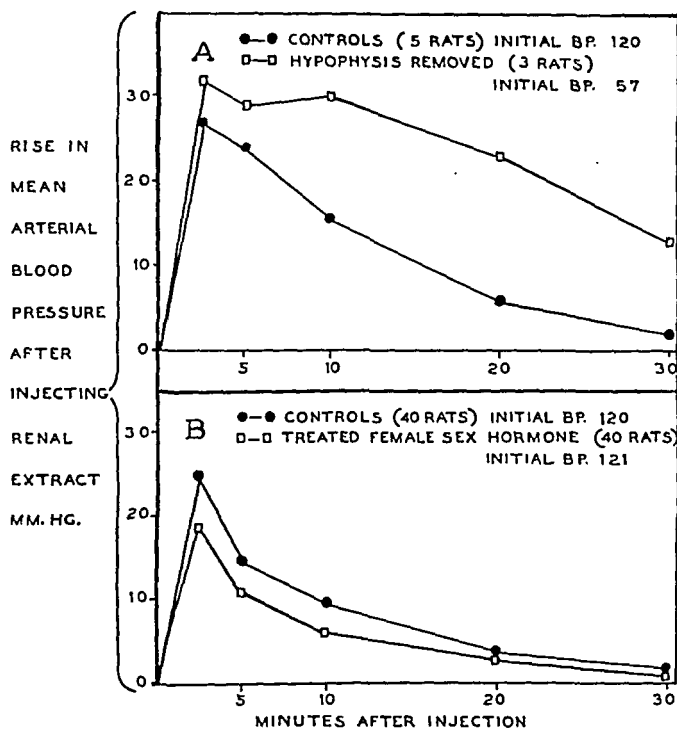


FIG. 4.—(A) Effect of removal of the hypophysis on the response to renin. This chart represents the averages of a day's experiments. The control blood pressures of the hypophysectomized rats are about half the pressures of the normal rats. The maximum response to renin is only slightly greater than in the controls, however their pressures remain elevated much longer. (B) Effect on renin response of treating rats with female sex hormones. This is the average of all the rats treated with esterin follicle-stimulating hormone and anterior pituitary-like hormone compared with their controls. The treated rats are slightly less sensitive than the controls, but the difference is small and of uncertain significance.

Twenty-two comparisons were made between the extracts of kidneys from normal rats and kidneys from hypophysectomized rats. No constant or significant difference in pressor property was

encountered, the kidneys of the normal animals having a greater effect in 5 instances, the reverse result being found 4 times, and the remaining comparisons yielding inconclusive results.

Observations on Castrated Animals. Two groups of castrated females were compared with normal females 2 and 5 weeks, respectively, after the removal of the gonads. Significant differences in the sensitivity to renin or in the amount of renin in the kidneys were not encountered. Similar negative results were obtained when a group of castrated males were compared with untreated control animals. Observations on rats which had been deprived of gonadic tissue for longer periods of time were not made.

Observations on Animals Treated With Sex Hormones. At the beginning of this study 5 female rats were on hand which had previously been treated for another purpose with injections of estrin (estradiol monobenzoate) for 2 months, followed by injections of the follicle stimulating hormone (castrate urine extract) and of the anterior pituitary-like hormone (follutein) for 5 days. It happened that control animals of the same age and size were not available at this time and these animals were compared with an equal number of older and larger controls. Marked differences were encountered between the treated and control animals. Attempts to confirm this result led to inconclusive findings. At a later date it was shown by Grossman and Williams⁵ that age was an important factor in the response of rats to the renal pressor substance. Our earlier experiments on the relation of these several sex hormones to renin were therefore repeated. Five animals were studied after receiving estrin (200 rat units daily) for 1 week, followed by follicle-stimulating hormone (in daily doses equivalent to 50 cc. of castrate urine) for 5 days and then anterior pituitary-like hormone (100 rat units daily) for 5 days. A second series of animals were treated similarly except that estrin was given for 2 weeks. A third series received estrin for 3 weeks, and so on, 8 groups of animals (5 rats in each group) being treated in all. Each group of animals was compared with controls of approximately the same size and age.

The results as regards the sensitivity of the animals are summarized in Figure 4 B, which presents the composite curve for 40 controls and 40 treated rats. On the whole, it appeared that the animals treated with the above mentioned sex hormones were slightly less sensitive than the normal animals; but the differences were not striking and there was much overlapping in the individual animals.

Seventy-eight comparisons were made as regards the renin content of the kidneys of those animals which received injections of the sex hormones and of the normal animals. Extracts from the treated rats gave the greatest effect 14 times, the reverse was encountered 15 times, and comparisons were inconclusive 49 times. Under the con-

ditions of our experiments treatment with the several sex hormones did not seem to alter the amount of renin in the kidneys.

Two series of rats were studied after they had received for 6 days the anterior pituitary-like hormone only. These animals showed no consistent difference from the controls as regards sensitivity to renin or as regards the amount of renin in their kidneys.

Discussion. It seems that the most significant of the findings which have been presented is the marked diminution in sensitivity of adrenalectomized rats to the renal pressor substance. Whether such insensitivity is in any way concerned with the hypotension of such rats is uncertain. At the present time, there is no convincing evidence for the view that renin plays a rôle in the regulation of normal blood pressure, and the fact that removal of both kidneys does not regularly lower the blood pressure suggests that the renal pressor substance is not concerned in the maintenance of normal blood pressure. Unless one makes the assumption that a relationship exists between the amount of renin released by the kidney and the normal level of the blood pressure, one has no right to attribute the hypotension of adrenalectomized animals to their insensitivity to renin. Regardless of this question, the observations on adrenalectomized animals constitute evidence in favor of the view that renal hypertension is dependent on renin. The increased blood pressure of animals with experimental renal ischemia disappears when the ischemic kidneys are removed (Blalock and Levy²). The hypertension of such animals also disappears when the adrenal glands are removed (Goldblatt,³ Page,⁷ Blalock and Levy²). Granting the possibility that the insensitivity of adrenalectomized animals to the renal pressor substance and the insensitivity of adrenalectomized animals to the substance responsible for the hypertension produced by renal ischemia may be purely coincidental, it is simpler to explain both of these phenomena by a single assumption, namely, that the increase in blood pressure brought about by renal ischemia is dependent on an increased rate of release from the kidneys of the renal pressor substance to which adrenalectomized rats are relatively insensitive.

Our data throw no light on the cause of the striking decline in blood pressure exhibited by the hypophysectomized animals. We do not know whether such hypotension was the result of removal of the anterior or the posterior lobe, because both were removed in our experiments. Such hypotension could not be the result of decreased sensitivity to the renal pressor substance because the hypophysectomized animals were somewhat more sensitive than the controls. The amount of pressor substance in the kidneys of the hypophysectomized animals was, as nearly as could be determined by our crude methods of assay, about the same as the controls. From the

data one can assume either: (a) that the hypotension of hypophysectomized animals is not related to the renal pressor substance; or (b) that if such a relationship exists it is mediated through some unknown mechanism.

The experiments throw no light on the disputed question of the relationship between the gonads and blood pressure. The questionable slight diminution in sensitivity of animals treated with the several sex hormones might seem to support the idea that "menopausal hypertension" in women is related in some way to decreased estrin production. However, our castrated animals failed to show increased sensitivity to renin, and furthermore, the difference between the normal animals and those treated with estrin did not occur in all groups and even on the average was of only slight degree. Our data do not justify any conclusions concerning the question of a possible relationship between alterations in gonadic activity, changes in the amount or effectiveness of the renal pressor substance, and the appearance of hypertension.

Summary. A study has been made of the relationship between renin, the pressor substance present in the kidneys, and certain endocrine glands. The following results have been obtained:

1. Adrenalectomized rats kept alive with salt solution displayed decline in blood pressure and were markedly less sensitive to renin than were normal animals.

These observations afford additional evidence for the assumption that the renal pressor substance is concerned in the production of hypertension brought about by renal ischemia.

2. The kidneys of adrenalectomized rats did not contain less of the renal pressor substance than did the kidneys of normal rats.

3. Hypophysectomized rats exhibited marked lowering of the blood pressure but were somewhat more sensitive to the renal pressor substance than normal rats. Hypophysectomy did not seem to alter significantly the amount of pressor substance in the kidneys.

4. Castration did not, under the condition of our experiments, appear to alter either the amount of renin in the kidneys or the sensitivity of rats to renin. Prolonged administration of several sex hormones caused inconstant slight diminution in sensitivity to renin without changing the amount of renin in the kidneys and without altering the blood pressure.

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AN EVALUATION OF THE INFLUENCE OF OVERWEIGHT ON BLOOD PRESSURES OF HEALTHY MEN.

A STUDY OF 3516 INDIVIDUALS APPLYING FOR PERIODIC HEALTH EXAMINATION.

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AMONG clinicians there is generally an assumption that overweight is a factor in the production of hypertension. A number of reports in the literature sustain this assumption. However, there is no general agreement as to the degree to which overweight may influence blood pressure nor has the attempt been generally made to evaluate and separate the important factor of age. It is generally conceded that, even in normal weight individuals, there is to be expected a moderate increase in blood pressure with advancing years. This is not so great as formerly assumed and most clinicians are inclined to believe that the systolic pressure should never exceed 150 mm. at any age, and that 135 mm. is more nearly the ideal in the later years of life. Two other factors which may well enter into the production of hypertension are both the degree and the duration of obesity. If obesity *per se* is indeed a factor in causing high blood pressure, it might well be expected that higher pressures will be associated with the higher degrees of overweight. Since it now appears fairly definite that duration of obesity is a factor in causing diminution of glucose tolerance,^{4,5} it is possible that it also has a part in the production of increased blood pressure. It is unfortunate that these contributory factors have usually been ignored in previous studies upon this subject.

The present study concerns 2858 cases of overweight men of various ages and an attempt has been made anew to evaluate overweight as a factor in hypertension. These individuals were ambulatory, about their usual occupations, and supposedly in good health. They applied for the periodic health examination provided by insurance companies carrying their several policies. They have been unselected for the study except for the factor of overweight. In this study, 658 cases of normal weight were added for control. Those having a systolic pressure of 150 mm. or higher were considered as having systolic hypertension and those having a diastolic pressure of 90 mm. or higher as having diastolic hypertension.

The cases were distributed into weight groups as follows: a "normal" weight group of those 5% under to 5% over "ideal"

weight; and overweight groups of 6 to 15%, 16 to 25%, 26 to 40% and 41% or more above "ideal" weight. The incidence of hypertension in these various weight groups is expressed in Chart 1.

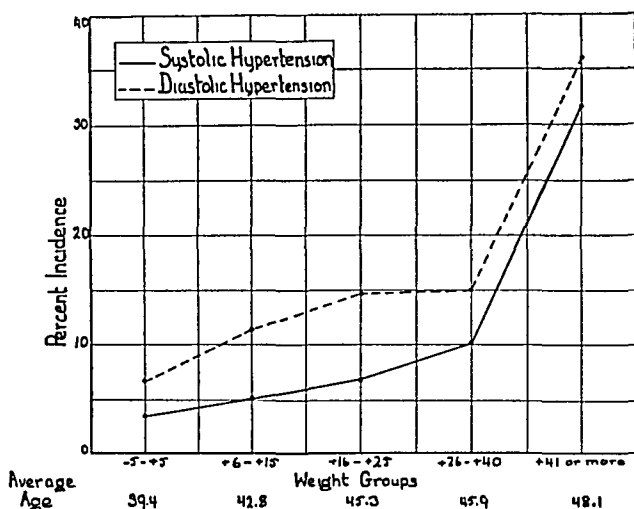


CHART 1.—Percentage incidence of systolic and diastolic hypertension in entire series of 3516 normal and overweight cases expressed in various weight groups.

For systolic blood pressure there was virtually no increased incidence among those of normal weight. There was, however, a moderately increased incidence for each overweight group up to 40%, at which point the incidence of hypertension was 10%, while in the group over 40% overweight there was a sharply increased incidence of hypertension to over 30%. The incidence of diastolic hypertension exceeded that of systolic hypertension in all ranges of overweight and, in general, showed a progressive increase to over 35% in the highest weight group.

Table 1 expresses average systolic and diastolic pressures for each of the weight groups. The systolic pressures advanced steadily from 119 mm. to 140 mm. with increasing weight. In the weight groups from 6 through 40% overweight there was little change in the average ages and an elevation of blood pressure averages from 122 to 127 mm. Average diastolic pressures generally paralleled the systolic.

TABLE 1.—AVERAGE BLOOD PRESSURES AT VARIOUS WEIGHT LEVELS.

Deviation from normal weight, %.	Average age.	Number of cases.	Systolic pressure.	Diastolic pressure.
- 5 to + 5	39.4	658	119.4	75.3
+ 6 to +15	42.8	1581	122.5	77.9
+16 to +25	45.3	915	125.0	79.7
+26 to +40	45.9	334	127.1	80.9
+41 and over	48.1	28	140.4	86.8

Chart 2 is a graphic expression of percentage incidence of systolic and diastolic hypertension for the normal weight and overweight groups taken separately in relation to age. Although there was a

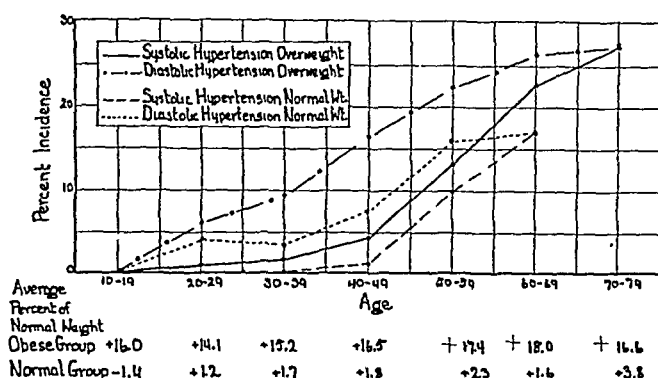


CHART 2.—Incidence of systolic and diastolic hypertension in normal and overweight groups.

striking parallelism in the lines, it will be noted that in the incidence of both systolic and diastolic hypertension the overweight groups exceeded the normal weight groups throughout the entire age span. Among the various age groups the maximum difference in average weight for the obese group was only 4%. The striking thing about this chart is the remarkable similarity of contour of the graphs for each group and the augmenting influence of overweight on hypertension at all ages.

Table 2 presents a contrast between average systolic and diastolic blood pressures in normal weight and overweight groups for each decade from 20 through 79. In general, the average systolic pressures were higher in the overweight group. This difference was greatest in the age groups from 50 to 59, where it amounted to over

TABLE 2.—CONTRAST OF AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES AT VARIOUS AGE PERIODS BETWEEN NORMAL AND OVERWEIGHT GROUPS.

Age.	Number cases.	Average % normal weight.		Systolic pressure.		Diastolic pressure.	
		Normal weight.	Overweight.	Normal weight	Overweight.	Normal weight.	Overweight.
20-29 . .	355	+1.2	+14.1	118.0	121.1	73.5	74.4
30-39 . .	1031	+1.7	+15.2	116.6	119.4	74.0	77.2
40-49 . .	1167	+1.8	+16.5	119.0	122.1	76.3	79.1
50-59 . .	684	+2.3	+17.4	117.8	129.2	77.4	81.3
60-69 . .	233	+1.6	+18.0	131.1	134.0	80.0	83.6
70-79 . .	33	+3.8	+16.6	126.5	131.6	79.5	80.0

11 mm. In the oldest age group, the systolic pressures definitely showed a falling off which possibly can be attributed to myocardial

impairment. The diastolic blood pressure likewise averaged higher in the overweight group. Again the greatest average difference occurs in the 50 to 59 age group where it amounts to approximately 4 mm.

Comment. Huber,² in a study of 1332 army officers in apparently good health, found that 18% of the overweight group had systolic pressures of 140 mm. or more. This group comprised 170 cases. He concluded that underweight and hypotension were much more closely associated than overweight and hypertension.

Our results differ sharply from those of Gager¹ in the incidence of systolic blood pressures of 150 mm. and above for the various decades of life. They are similar to Gager's in the fact of a preponderance of hypertensives in the overweight group, but the percentage incidence in our study was much less. For instance, Gager found that 28.3% of his obese patients for all ages showed systolic hypertension as against our 6.5%, and 16.4% at all ages for the normal weight group as against our 2.6%. The only explanation we have for this decided difference is that his cases were selected from the Cornell Clinic and the observations presumably were made upon sick individuals whereas our study has been made upon presumably healthy individuals. It is unfortunate that Gager did not classify his patients as to the degree of overweight. Symonds⁶ found an average rise of only 8 mm. for a group 50% overweight.

Overweight in this study has shown a very definite and positive influence in the production of increased incidence of hypertension. This incidence is more marked in the diastolic than in the systolic blood pressure. The study unfortunately does not contain the extreme degrees of overweight where it might be presumed that the incidence of hypertension would be even greater. Average blood pressures were consistently higher in the overweight group, but, in the cases studied, not so great as had been expected. We are inclined to agree with Mosenthal³ that the influence of overweight on blood pressure has probably been somewhat exaggerated.

Summary and Conclusions. A study of the association of systolic and diastolic hypertension with overweight has been made on 2858 cases of healthy individuals who applied for a periodic health examination; 658 normal weight cases were used as control. The factor of age has been considered.

In this group of cases, overweight appeared to exert a positive influence in causing increased incidence of hypertension. This was more marked in the diastolic phase.

The difference in average blood pressures was greatest in the age group from 50 to 59.

The incidence of hypertension in the overweight group was generally lower than reported by other observers.

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FURTHER STUDIES ON THE TREATMENT OF CHOREA AND RHEUMATIC INFECTION BY FEVER INDUCTION.

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A STUDY of the results by fever induction treatment used in an effort to relieve rapidly the symptom of chorea brought to light data confirming impressions gained in the management of these cases over a period of years. The origin of a number of misunderstandings that have crept into the literature seems to be explained by methods of approach in study and in the management of chorea as a whole.

This study is based entirely upon a group of cases ranging in age from 4 to 15 years. The first impression gained is the need for careful previous history even in the very young child and careful neurologic investigation before a definite diagnosis is made. The cases analyzed here postdate those reported in 1933 by Capper and Bauer¹ and all of them occurred prior to 1936. Cases seen in 1937 and 1938 are not included since their fate cannot as yet be indicated except by inference.

A diagnosis of chorea was made on 85 cases; 4 of these proved to have brain tumors, were operated upon, and the diagnosis verified; 4 had epidemic encephalitis, 7 were distinctly corpus striatum lesions with athetoid movements and were in no way related to chorea. All of these had erythrocyte sedimentation tests under 12. These 15 cases are not included in this report further but are referred to simply to show the ease with which mistaken diagnoses can be made and to call attention to the harm that might be done if fever induction therapy is used before diagnosis is certain. One hesitates to visualize what would happen to a patient with a growing brain tumor if fever induction were used instead of neurosurgery. Anyone familiar with encephalitis knows the untoward results following exposure to sunlight and heat. Careful experimentation has shown that athetoid movements of cryptogenic origin are never favorably affected by fever induction therapy.

With these subtractions we are left with 70 cases with choreiform movements for analysis and treatment. Breaking down this group of 70 their histories revealed the following:

- 12 had previous attacks of chorea, 9 of whom had heart lesions upon admission;
- 7 had multiple definite attacks of rheumatic infection including heart lesions;
- 5 had muscle pains without other symptoms;
- 1 had peritoneal irritation and epistaxis, no history of any other lesion and no cardiac involvement upon admission or discharge;
- 1 had joint pain admitted with a heart lesion;
- 18 had no previous history but a heart lesion upon admission;
- 16 had no previous history but had a muffling of the first sound upon admission. Seven of these were discharged from the ward with definite heart lesions. (See ultimate results later.)
- 10 gave no previous history of rheumatic infection, chorea, or any suggestion thereof, nor did they have heart lesions upon discharge.

Twelve of these 70 cases had palpable rheumatic nodules.

Thus in 70 cases heart involvement was clinically evident some time or other in 51; 35 were definitely damaged in earlier rheumatic episodes before attending our clinic, and 16 were involved primarily. From the standpoint of heart disease prevention we were successful up to the time of discharge in 9 of these 16 patients. Four of the remaining 7 showed no lesion after 2 years' observation, 1 of the remaining 3 had a second attack of chorea within a year with continued heart involvement, and the remaining 2 had mitral systolic murmurs with ample cardiac reserve. Therefore, of 16 cases of chorea with beginning or early heart involvement 13 completely recovered, two hearts are scarred but recovered, and but one is damaged with a recrudescence of chorea present. Of the 35 secondary cases, cardiac salvage is operating in a large proportion with encouraging results. An analysis of this at the moment would take us too far afield.

Fever induction therapy was practiced in all 70 cases. Five of these (children) were treated by a competent physiotherapist using the diathermy machine to induce fever. The patients responded quite as well from the standpoint of the amelioration of the choreiform movements as with other methods of fever induction. A greater number of children were not subjected to this treatment because they could not be controlled sufficiently well to keep them in the apparatus and adequate febrile reactions could not be obtained. This method therefore is held in reserve for older, more readily controlled patients rather than abandoned entirely.

In 65 cases, fever induction was practiced by means of typhoid paratyphoid vaccine administered intravenously as suggested by Sutton.³

Technique is as follows: Three and one-half hours following a light breakfast a hypodermic injection of morphine sulphate is administered, the dose depending upon the age and weight of the patient. One-half hour later an intravenous injection of 0.2 cc. of a mixed typhoid paratyphoid vaccine is given. To each cc. there are 500 million typhoid and 250 million each of paratyphoid A and B in the preparation used. Special preparations on the market with proteins removed are not as effectual as the regular stock vaccine.

The patient is wrapped snugly in blankets. An experienced nurse specials the patient and the temperature is taken at 10-minute intervals. A temperature of at least 104° F. must be obtained for the best results and remain there for 2 hours. If it tends to go over 105° F. the patient should be removed from the blankets and the temperature allowed to come down. If it does not rise to 104° F., a second intravenous injection of the same dose should be given as it descends. When the patient is out of the blankets he is ready for a hearty lunch.

Daily treatments for 8 days constitute the course for the average child. In the event that the original dose has not induced the desired temperature the dose is increased the next day 0.1 or 0.2 cc. In the exceptional case, it has been necessary to give as high as 1.5 cc. for the eighth treatment. Marked improvement is noted after the third or fourth treatment. In instances where the temperature has gone to 106° F. it has been noted after one treatment. A few have residual minor evidences after the eighth treatment which seem to clear up entirely after a week's rest.

Results. Speech improves after the third or fourth injection quite rapidly using test words such as "municipal" and "Methodist Episcopal." A permanent record of improvement is noted on the chart by the daily signature of the patient beginning on the day of admission as suggested by Gerstenberger.² The signature shows a decided improvement after the third or fourth injection.

A few cases are recalcitrant to the extent of needing a second and even a third series of treatments. In this group of 65 cases 5 were given 2 series and three 3 series. Eight days are permitted to elapse between series.

Two patients alone showed untoward reactions. Their temperature rose to 107° F. with extreme rapidity accompanied by evidence of collapse. Adrenalin hydrochloride 1 to 1000 in 2 to 5 m doses and an ice water enema gave prompt relief. The adrenalin hypodermic is prepared and ready for use at all times that the patient is under active treatment. There has been no evidence of any deleterious after-effects following fever induction in any of our series.

Fever induction therapy, as far as we can determine, does not influence any other manifestation of rheumatic infection. Therefore these patients must be subjected to such other antirheumatic measures as are at our command. Despite the amelioration of the outstanding symptom, chorea, we do not make the mistake of discharging these patients as cured and permitting them to assume normal activities simply because chorea has disappeared. We believe that this practice in other clinics has been followed by an increased

gravity in heart involvement and indeed perhaps heart involvement in instances where it should not have occurred. The tendency is to blame fever induction for this increase in heart damage whereas our foregoing data indicates no such thing and with improved technique our later experience convinces us that an even better record is being made in our more recent years.

The plan followed for these patients throughout the course of their illness in addition to fever induction therapy parallels our treatment of rheumatic infection excepting in the maniacal or delirious chorea upon admission. In these latter, if not controlled with phenobarbital and sodium bromide, lumbar puncture is practiced. The patients are kept at rest. We, like our English contemporaries, regard sodium salicylate as a mildly specific drug in rheumatic infection. It does seem to do more than simply relieve joint pains. The dose must be large amounting to at least 5 gm. daily accompanied by an equal or larger amount of bicarbonate of soda given in divided doses. Acetylsalicylic acid is a futile substitute. Since nausea and vomiting are due to acidosis and not irritation following the use of sodium salicylate, in addition to the bicarbonate of soda the diet employed is high in carbohydrate and low in fat. There is no trouble encountered in using these large doses.

The criteria for determining quiescence of the rheumatic attack are as follows: (1) Consistently normal temperature; (2) no cardiac dilatation or increase in pulse rate; (3) no peritoneal, muscular, or joint involvement; (4) erythrocytic sedimentation rate not faster than 12 at the end of 2 hours.

Every one of these 70 cases had undoubted rapid sedimentation rates upon admission. Careful study will reclassify supposed choreics with normal sedimentation rates in other disease groups as indicated earlier in this discussion. The sedimentation rate became normal in this group of cases in 2 instances in 1 month and in 1 in 6 months. The average is $2\frac{1}{2}$ to 3 months.

All children with chorea or other rheumatic involvement are kept at rest in bed and on salicylates until all of these criteria are satisfied. Then massage followed by graduated exercise is tried, the pulse rate and temperature being the guide for increase. Iron tonics are given. Whether cardiac involvement is noted or not, this program is continued until the child shows evidence of ability to resume the normal activities of a child of its age. It is watched for evidence of decompensation, recurrence of rheumatic or choreic manifestations, and intercurrent illnesses.

We have been in the habit of giving a course of salicylates for 1 week every month for over a period of 1 year. Being cognizant of the fact that so many American observers assert that this drug is effective only in the relief of the exudative and not the proliferative lesion of rheumatic infection it is necessary to present an excuse for

this procedure. It is our contention that the drug is feebly specific in the proliferative lesion and its use in large dose both in the choreics and in the rheumatics not presenting this symptom has resulted in a greater rapidity of improvement compared with cases where it has not been used. Furthermore, the return to normal sedimentation rates has been relatively more rapid. We have also had fewer recurrences of rheumatic infection or chorea following this general plan.

Cardiac decompensation on the other hand has not occurred where this procedure has been carried out, so that we cannot dogmatically state that the use of the salicylates in themselves has been effectual or just how great a part they do play.

The whole health program sketchily outlined above plays some part in this problem of recurrence and it is impossible to say how much or how little the use of drugs or any other one element operates as a preventive measure. Suffice it that the prevention of recurrences and lessened degree of heart involvement under this régime is impressive both in chorea and in rheumatic infections without evidence of chorea.

In the light of statements made informally by other observers that there is an increased cardiac involvement in the number of choreics treated by fever induction therapy, our experience is a direct contradiction. The only inference that we can draw, as already stated, is that in the light of the rapid recovery from choreic manifestations the rheumatic background may be ignored, the child regarded as recovered prematurely, undue activities permitted too early, the child discharged before it has entered a truly quiescent stage, and it may not be adequately supervised over a long enough period to insure against secondary activation of proliferative lesions. This follow up as we have outlined it at the present moment is the essence of real heart disease prevention. Unfortunately, in our series we have a large group of children, 35 in number, whom we did not see in their primary illness, hence we were compelled to employ this method in what might be termed heart salvage which is inexplicably confused with heart disease prevention in most clinics.

Summary.—From this and our earlier series of cases of chorea we feel justified in averring that fever induction is an important and valuable addition to our therapeutic armamentarium. The danger in its use, that is, collapse and cardiac dilatation, can be eliminated by expert application of the method. True chorea in childhood is generally rheumatic in origin. Care in diagnosis will prove this. The need for antirheumatic treatment and management is necessary for a complete ultimate recovery for these patients.

The use of sodium salicylate in large doses is helpful. The erythrocyte sedimentation rate is a valuable guide in determining rheumatic activity or quiescence and is as consistent in the choreic

as in the non-choreic rheumatics. The management of the patient as a potential rheumatic in the quiescent period must be carried out over a long period of time and the methods of such management must be improved upon generally. It is hoped that the suggested plan practiced by us will prove a step in this direction.

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NOTE ON ORAL ADMINISTRATION OF POTASSIUM CHLORIDE IN THE TREATMENT OF HAY FEVER, NASAL ALLERGY, ASTHMA AND SINUSITIS.

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BENSON BLOOM¹ has recently reported on the oral administration of potassium salts in hay fever and asthma. He indicates that other allergic conditions may be benefited by treatment with potassium salts.

Dosage and Method of Administration. The doses for children of various ages are indicated in Table 1. The following cautions should be observed in administering the drug: Potassium chloride should be dissolved in distilled water and administered in teaspoonful doses, well diluted. It may be given in orange juice or other fruit juice before meals. *Dilution of the medication is important.* Abdominal distress and epigastric pain were not complained of when this method was followed. Syrups or other vehicles should be avoided. Potassium chloride should not be given in capsules, tablets or powder, in undiluted form. Sodium chloride intake should be limited during the period of treatment. Potassium salt is contraindicated in patients suffering from renal disease with diminution of potassium chloride excretion, or in those suffering with adrenal insufficiency. No toxic effects were noted either by Bloom or myself.

Clinical Use. The most striking results were obtained in children suffering from hay fever combined with asthma. A remarkable example was a 2-year-old child dyspneic and cyanotic, with wheezing and continuous cough. Within 12 hours after the administration of 1 grain of potassium chloride solution every 4 hours, the dyspnea, cyanosis, cough and wheezing disappeared. Satisfactory results were also obtained in patients suffering from allergic rhinitis. After 3 to 5 days' treatment with potassium chloride, the nasal mucous membrane had lost its pale, boggy appearance, the edema of the turbinates decreased and the watery nasal discharge ceased.

The cases of sinusitis observed were either chronic or followed acute upper respiratory infections. In several patients suffering

TABLE 1.—RESULTS OF USE OF POTASSIUM CHLORIDE IN ALLERGIC STATES.*

(A) Hay Fever Without Asthma.

Name.	Age (years).	Date, 1938.	Dosage, grains t.i.d.	Results.
F. A. (sister of J. A.)	18	10-30	5	Hay fever improved within 48 hrs.
Mrs. A.	..	10-30	5	Sneezing and eye symptoms greatly diminished within 72 hrs.
Mrs. J. A.	..	10-21	5	No sneezing or nasal congestion after 24 hrs.
Mrs. S. (Mother of H. S. and N. S. under Hay Fever With Asthma.)	..	10-25	5	Sneezing, nasal congestion greatly diminished after 24 hrs.

(B) Hay Fever With Asthma.

J. D.	5	10-20	2½	Stopped wheezing within 48 hrs.
P. P.	6	10-21	2	Refused to take in water. Wheezing relieved when given in orange juice.
J. U.	5	10-24	3	Severe wheezing with dyspnea. Marked improvement in 24 hrs. Wheezing disappeared in 48 hrs.
N. S.	4	10-25	1½	Refused to take in plain water. Dissolved in orange juice. Wheezing disappeared and symptoms cleared in 24 hrs.
H. S.	7	10-25	3	Same as above.
M. A.	2	10-31	1	Severe exudative diathesis, eczema and asthma. Wheezing stopped after 24 hrs. Previously difficult to control with adrenalin and ephedrin.
J. A.	14	10-30	4	Wheezing decreased within 48 hrs.
B. H.	10	11-5	4	Severe asthma. Greatly improved in 24 hrs. Wheezing stopped in 48 hrs. Has always been difficult to control with adrenalin and ephedrin.
R. D.	10	11-9	4	Wheezing stopped in 48 hrs.

(C) Allergic Rhinitis.

M. W.	8	11-7	3	Pallor and turgescence of mucous membrane disappeared after 4 days.
R. D.	10	11-9	4	Excessive nasal secretion diminished within 3 days.
M. K.	10	11-11	4	Nasal obstruction and secretion cleared after third day.
M. K., Jr.	7	11-15	3	Mucous membranes pink and edema disappeared after 5 days.
E. W.	3	11-14	2½	Relieved of nasal obstruction after 48 hrs.
G. D.	8	12-15	3	Also had slight wheeze which cleared within 48 hrs.

(D) Sinusitis.

M. P.	6	10-21	2½	Roentgen ray showed definite cloudiness over maxillary sinus. Relieved of nasal congestion after 72 hrs.
A. F. A.	..	10-20	5	Maxillary sinus tenderness. Relieved after 48 hrs.
Mrs. M.	..	10-22	5	Chronic sinusitis. Relieved after 48 hrs.
W. G.	..	10-23	4	Chronic sinusitis with nasal polyps. Relieved.
J. L.	13	11-15	4	Subacute sinusitis aggravated by use of argyrol. Congestion relieved after 24 hrs.
J. H.	12	12-1	4	Chronic sinusitis for over 1 mo. Relieved after 48 hrs.
F. A.	8	12-1	4	Improved after 48 hrs.
M. K.	6	12-15	3	Relieved of chronic catarrhal nasal congestion with tenderness over maxillary sinuses.

* Results of any hay fever treatment begun no earlier than October 21 are useless in evaluating that treatment.—EDITOR.

from sinusitis, the alleviation of the maxillary tenderness and of nasal fulness and discomfort was striking, after the administration of potassium chloride. The nasal discharge became thinner and less tenacious in character after several days' treatment with potassium chloride. Allergy probably is a factor in some cases of sinusitis.

The alleviation of symptoms of hay fever with asthma, allergic rhinitis and sinusitis here reported was striking.

The exact pharmacologic mechanism is not clear, though Bloom thinks the clinical effect depends on the potassium ion of the salt. Stoesser and Cook² have shown that diminished sodium chloride intake in asthmatic children decreased symptoms, while addition of sodium chloride during a period of remission caused the symptoms to reappear. These authors conclude that, "asthma may be aggravated by sodium chloride and mitigated by depletion of body salts, even in the presence of excessive hydration."

In the series of cases here reported, no determinations were made of the sodium or potassium content of the blood or of the excretion of these elements in the urine. However, a mild diuresis occurred following administration of potassium chloride to several of the patients here noted. Perhaps the action of the potassium ion is a displacement of the sodium ion in the tissues, which produces a local tissue dehydration. This may explain the decrease in turgidity of the nasal mucous membrane in allergic rhinitis, and may account for the relief and improved drainage obtained in sinusitis. The exact pharmacologic action of the potassium ion in these conditions deserves further intensive study.

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LYMPHOGRANULOMA VENEREUM: TREATMENT OF 300 CASES.

WITH SPECIAL REFERENCE TO THE USE OF FREI ANTIGEN INTRAVENOUSLY.

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THE treatment of lymphogranuloma venereum has received only scant consideration in the literature up to the present time. Each of the several clinical entities now embraced by this disease has various forms of therapy described for its individual cure or palliation. When

lesions such as local adenopathies, generalized adenopathies and rectal conditions were coördinated into one disease picture, attempts were made to use a single agent for the cure of all manifestations. Thus, Hellerstrom,⁹ recognizing the systemic nature of this disease, used the Frei antigen intravenously as early as 1931 in one case. Among others, chemical agents such as tartar emetic, fuadin, gold salts, emetine and the arsenicals, were tried. Foreign protein therapy, Roentgen ray therapy, and attempts at immunization with Frei antigen have been used with varying degrees of success. Systemic manifestations of the disease have been stressed and clinically described by Eberhard² and Gutman.⁷ To combat these is of primary importance in an effort to arrest the disease process wherever it may manifest itself in the body. The adjuvant methods, radical surgical or local conservative, are then likely to become useful and effective.

This report deals with the treatment of 300 consecutive cases of lymphogranuloma venereum. A group (207) of this series received Frei antigen intravenously, while the remainder (93) received the various types of therapy suggested by other authors.

Frei Antigen Therapy. Frei antigen was used intracutaneously in the treatment of lymphogranuloma in 1927 by Gay Prieto.⁵ The fact that amelioration of symptoms occurred when the skin test was performed led to the use of this method. A report of treatment of 200 cases by Wien and Perlstein¹⁶ represents the largest single series of cases among whom this type of treatment was used. The results reported are encouraging. This method, however, has its objection in that a positive intracutaneous reaction occurs with each successive injection. It was not found possible to alter the Frei reaction from positive to negative even after a series of 60 to 70 injections. This fact has been confirmed repeatedly.

The intravenous route offers a faster, more effective and less objectionable way of using this form of treatment. Frei antigen intravenously has been used in this group of cases since 1934, and about 3500 intravenous injections have been given to 207 patients to date. With the exception of a small number confined to the hospital the treatment was given to ambulatory patients. A routine method was found sufficient and effective in all cases. This consisted of the intravenous injection of 0.3 cc. of Frei antigen 3 times a week on alternate days. There were no untoward alarming symptoms due to therapy in any case. No embolic phenomena were observed, in spite of the fact that free particles could be seen in the fluid used intravenously.

Type of Antigen. The sources of human antigen are uncontaminated suppurative buboes which have not broken through the skin. Aspirated material can be used filtered or unfiltered after the usual preparation, suggested by Frei.^{4a} The human unfiltered antigen was used throughout the entire group for both diagnosis and therapy.

Reactions After Intravenous Treatment. As a rule, only the first and second injections of the Frei antigen produce definite symptoms. These are a chill, fever, malaise, occipital headaches, occasionally nausea and vomiting; infrequently a generalized maculo-erythematous rash which fades in 48 hours; and in some cases joint pains. The succeeding injections produce only headaches and malaise, but are therapeutically as effective as the initial doses, despite the lack of a severe systemic reaction. The initial intravenous injection into 12 patients unaffected by lymphogranuloma produced no reaction whatever.

With some modifications the experience of the author is very similar to that of Gay Prieto and Egea Bueno.⁵ Four main types of reaction may take place after the initial injection (Fig. 1): *A*, the prompt reaction; *B*, the delayed reaction; *C*, the delayed protracted; and *D*, no reaction, "anergic reaction." A fifth type, a successive repeated reaction, is very unusual.

A prompt reaction (Chart A) occurs in 2% of the cases. It begins about $\frac{1}{2}$ to 1 hour after the injection. The patient gets a severe chill which may last from 20 minutes to 4 hours. This is associated with marked perspiration and prompt rise in temperature to 103° or 104° F. In one case the temperature rose to 106° F. The temperature subsides within a period of 24 hours. During this time the patient complains of occipital headaches which may persist for from 18 to 36 hours. Occasionally there is nausea and vomiting. Focal reactions take place: the inguinal glands when enlarged become more tense, fluctuant inguinal abscesses occasionally break open and discharge profusely, and the pain in the inguinal swellings becomes more pronounced at the height of the reaction. Within 24 hours all of these manifestations subside to a remarkable degree, the swelling recedes and the local pain stops. Patients with rectal or genital involvement report a distinct change in symptoms. The purulent and bloody discharge becomes less. The local pain and tenderness practically disappear. Local examination, however, reveals little anatomic improvement. The constitutional symptoms likewise show a marked improvement. The feeling of malaise, headache, and muscle pains, occasionally joint pains promptly subside.

A delayed reaction (Chart B) is the most common, occurring in about 68% of cases. It begins about 10 to 12 hours after the injection and lasts for 12 to 24 hours. The reaction is identical with that described above for the immediate reaction, with the exception of the difference in the later time of onset. The fever and constitutional reactions subside at the end of a 24-hour period.

A delayed protracted reaction (Chart C) is observed in 4% of the cases. The patient feels no untoward effects for about 24 hours after injection. The reaction then commences with a severe chill which may last for $\frac{1}{2}$ to 2 hours and is accompanied by a fever up

to 106° F. These symptoms will not subside completely until the end of the fifth day after the initial injection.

Anergic reaction (Chart D). This type of reaction occurs in about 25% of the cases seen. The patient is entirely unaffected by the injection of the Frei antigen from the very beginning.

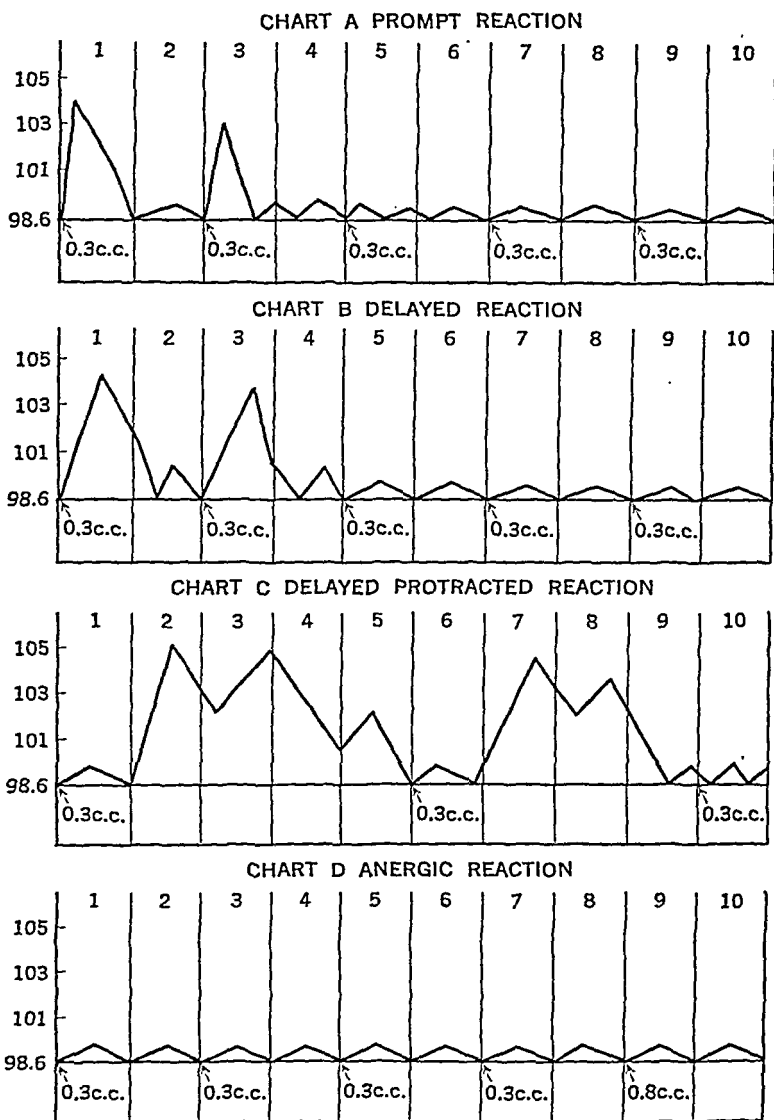


FIG. 1.—Types of fever curves following the intravenous use of Frei antigen.

In two of our patients a severe reaction of the delayed protracted type occurred each time the Frei antigen was given intravenously. Fortunately, this type of reaction is very unusual.

When the *second dose of antigen* is administered, after 48 hours, the chill, fever, and headache, repeat themselves in a manner similar to that after the initial injection. The reaction is, however, not as violent.

A *change of antigen* in the course of treatment may or may not produce a repetition of the initial reaction. The potency of the new antigen used and the extent of the patient's disease come into consideration when a new antigen is substituted.

Results of Treatment. For purposes of discussion, our cases may be divided into three groups: those with glandular, those with rectal, and those with genital lesions (Tables 1 and 1A). It must be remembered that lymphogranuloma venereum is venereal in origin and that a patient having this disease may also be suffering from one or more of the other known venereal diseases. Thus, only about one-half of our series showed uncomplicated lesions due to lymphogranuloma alone, while the remainder showed two or more coëxisting diseases (Table 2). Treatment of the primary lesions, which usually are in the form of small ulcerations on the genitalia or a urethritis, is negligible, since the lesions (commonly overlooked) heal invariably of themselves within a period of 2 weeks.

TABLE 1.—LYMPHOGRANULOMA VENEREUM. CLASSIFICATION.*

	Grand total.	Male.			Female.		
		Total.	Wh.	Col.	Total.	Wh.	Col.
Glandular . . .	186	172	66 (11)	106	14	1	13
Rectal . . .	55	23	23 (3)	0	32	12 (9)	20
Genital . . .	59	33	3	30	26	2 (2)	24
Total . . .	300	228	92 (14)	136	72	15 (11)	57

* The figures in parentheses refer to natives of Puerto Rico.

TABLE 1A.—LYMPHOGRANULOMA VENEREUM. RACE.*

	Total.	%.
White	107 (25)	35 (8)
Colored	193	65
Total	300	100

* Figures in parentheses refer to natives of Puerto Rico.

TABLE 2.—LYMPHOGRANULOMA VENEREUM. CASES ASSOCIATED WITH OTHER VENEREAL DISEASES.

Diseases.	Total No.	Cases with 1, 2, 3 and 4 diseases.	%.
Lymphogranuloma	157	157	52.3
Lymphogranuloma and syphilis	71	99	33
Lymphogranuloma and gonorrhea	26		
Lymphogranuloma and chancre	2		
Lymphogranuloma, syphilis and gonorrhea	35	42	14
Lymphogranuloma, syphilis and chancre	6		
Lymphogranuloma, gonorrhea and chancre	1		
Lymphogranuloma, syphilis, gonorrhea and chancre	2	2	0.7
Total	300	300	100

CASES WITH GLANDULAR LESIONS. This group includes those having inguinal, femoral and pelvic adenopathies. Of 186 cases, 111 (60%) subsided without abscess formation (Table 3); and 75 (40%)

TABLE 3.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 111 CASES WITH NON-SUPPURATIVE ADENOPATHY.

Classification.	No. of cases.	Sex.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Av. No. of inj.	Results.			Pos. Wass.	Pos. G. C.	Pos. Durey.	
								Excellent.	Good.	Poor.				
A. Inguinal unilateral	40	M	28	6 wks.	Frei antigen Excision None	29 4 7	7 wks. 6 mos. 8 mos.	8	27	2 4 7	12	7	2
B. Inguinal bilateral	21	M	30	6 wks.	Frei antigen Excision None	12 2 7	6 wks. 6 mos. 8 mos.	8	11	2 2 7	1	9	6	
C. Inguinal unilateral with penile primary	15	M	33	4 wks.	Frei antigen Excision	14 1	4 wks. 4 mos.	7 ..	10 ..	3 ..	1 1	5	3	2
D. Inguinal bilateral with penile primary	12	M	26	6 wks.	Frei antigen None	10 2	6 wks. Unkn.	11 ..	8 Un	.. known	2 ..	8	7	
E. Inguinal bilateral with urethritis	4	M	28	6 wks.	Frei antigen Excision	3 1	8 wks. 4 mos.	16 ..	1 ..	2 1				
F. Inguinal bilateral with vulval primary	10	F	26	4 wks.	Frei antigen None	6 4	4 wks. Unkn.	6 ..	6 4	4	3	
G. Inguinal bilateral with bubonuli	3	M	28	4 wks.	Frei antigen Tartar emetic	2 1	4 wks. 3 mos.	11 10	2 1	1		
H. Generalized simulating infectious mononucleosis	3	M	28	3 wks.	Frei antigen Incision	2 1	6 mos. 5 mos.	15 ..	1 ..	1 1	1	1	
I. Inguinal with granuloma symphysis pubis	2	M	23	1½ yrs.	Frei antigen	2	8 wks.	16	1	1	..	1		
J. Generalized with primary lesion on finger	1	M	16	3 wks.	Excision	1	3 mos.	1				

went on to suppuration (Table 4). This percentage is definitely less than the usual 60% suppuration reported by most authors. Early diagnosis and prompt therapy undoubtedly contributed to this reduction. The deep inguinal and pelvic adenopathies offered no difficulties since all of them subsided without suppuration. No case of generalized peritonitis from suppurative pelvic adenopathy has thus far been reported. The type of therapy and comparative results in the treatment of the suppurative and non-suppurative groups are recorded in Tables A and B.

The term "healed" refers to absence of constitutional symptoms, and disappearance of clinical signs of actual disease in a period of average optional duration of treatment, that is, 6 weeks in the inguinal group treated with Frei antigen. The term "good result" implies healing in a period of about 3 months without resort to any other

therapeutic measure. Poor results are used to denote cases which required longer than 3 months for healing.

TABLE A.—NON-SUPPURATIVE ADENOPATHIES—111 CASES.

	No. of cases.	Duration of symptoms (wks.).	No. of injections.	Results.		
				Healed.	Good.	Poor.
Frei antigen	81	6	9	68	9	4
Excision	10	24	8	2
Tartar emetic	1	12	1
No treatment	19	32	17	2

TABLE B.—SUPPURATIVE ADENOPATHIES—75 CASES.

	No. of cases.	Duration of symptoms (wks.).	Duration of treatment (wks.).	No. of injections.	Results.		
					Healed.	Good.	Poor.
Frei antigen	62	9	8	11	51	8	3
Excision	2	5	12	..	1	1	
Incision and drainage . . .	9	9	20	..	1	1	7
Tartar emetic	1	5	4	1
None	1	5	?	1	

Cases receiving Frei antigen intravenously showed the best results, as 119 of 143 healed in 6 weeks (83%) with or without suppuration and sinus formation. To this group may be added 17 cases (12%) which took 3 months to heal. A very significant fact is that over a period of 2 years it was not found necessary to incise and drain or excise a single case of suppurative or non-suppurative adenitis observed. Aspirations, where indicated, and Frei antigen intravenously were found adequate. These results compare exceedingly favorably with those of Prehn¹⁴ who reports that incision was done in about 75% of his cases, necessitating hospitalization of from 6 to 38 weeks.

Thus, it may be stated that when no treatment was instituted, about 25% of cases healed spontaneously within the period of 6 weeks which was the average optimal time of any therapy used. When any method mentioned above was used all of the cases had healed at the end of 8 months of observation in a series of 60 cases.^{10a} Excision of all diseased tissue is often impossible. In about one-third of the cases, retroperitoneal enlargement accompanies the evident inguinal adenopathy. The fact that elephantiasis of the genitalia may take place after a complete removal of the inguinal nodes also militates against this procedure. However, in 12 cases of block excision an average of 5 months' observation and treatment was

necessary and the results were good in 10 of the 12 cases. There was no evidence of genital elephantiasis in this group when followed up.

TABLE 4.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 75 CASES WITH SUPPURATIVE ADENOPATHY.

Classification.	No. of cases.	Sex.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treatment.	Av. No. of inj.	Result.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
								Excellent.	Good.	Poor.			
A. Inguinal unilateral	6	M	37	5 wks.	Frei antigen None	5 1	4 wks. Unkn.	9 ..	3 ..	2 1	1 1	1
B. Inguinal bilateral	7	M	27	4 wks.	Frei antigen	7	7 wks.	15	6	1	..	1	2
C. Inguinal unilateral with penile primary	9	M	27	5 wks.	Frei antigen Excision	6 3	6 wks. 5 mos.	9 ..	4 1	2 1	1 1	1	1
D. Inguinal bilateral with penile primary	4	M	28	1½ yrs.	Frei antigen Incision	2 2	4 wks. Unkn.	7 ..	2 ..	2 2	2	
E. Inguinal unilateral with spontaneous sinus	22	M	29	5 mos.	Frei antigen Incision	19 3	7 wks. 4 mos.	11 ..	10 ..	3	7	6
F. Inguinal bilateral with spontaneous sinus	5	M	28	6 mos.	Frei antigen Incision	3 2	3 wks. Unkn.	7 ..	3	2	1
G. Inguinal unilateral with sinus and penile primary	4	M	35	6 wks.	Frei antigen	4	17 wks.	16	..	4	..	1	2
H. Inguinal bilateral with sinus and penile primary	10	M	31	5 wks.	Frei antigen Tartar emetic Incision	8 1 1	3½ mos. 1 mo. 3 mos.	25	5	3 1 ..	6	6
I. Inguinal bilateral with urethritis	4	M	23	3 wks.	Frei antigen	4	7 wks.	14	4	2	2
J. Inguinal bilateral with vulval primary	4	F	28	3 mos.	Frei antigen	4	8 wks.	8	4	2	

Until recently the treatment of the inguinal lesions presented a surgical problem. At present, it may be stated that the problem is that of treating a systemic condition with local manifestations and that conservative methods are by far the most commendable in this group. The treatment recommended is the use of Frei antigen intravenously with aspiration of local suppurative foci where indicated.

CASES WITH RECTAL LESIONS. The natural course of the lesions is one that leads to chronicity. The average duration of disease at the time of examination is about 3 years. The various manifestations may be seen in Tables 5 and 6. It is noteworthy that among the 23 males, the largest group, 12 (52%), was due to pederasty. This group represents cases with primary implantation of the disease in the rectal wall. There is, however, ample proof that the rectal lesions may develop as a result of previous primary genital lesions and a secondary spread to the pelvic lymphatics by direct extension through the femoral and inguinal canals.^{10b} The rectal lesions were tubular in type in 32 out of 55 cases (58%). This tubular group represents persistent subacute and chronic lesions,

while the diaphragmatic type, 23 cases (42%), represents more of the healed type of fibrous stricture.

TABLE 5.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 23 MALES WITH RECTAL LESIONS.

Classification.	No. of cases	Average age.	Type.		Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Results.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
			Tub.	Dia.					Excellent.	Good.	Poor.			
A. Chronic proctitis, rectal stricture due to pederasty	12	43	9	3	5 yrs.	Frei antigen	11	18 wks.	19	..	3	7		
						Dilatation	2	18 wks.	2	..	6	2
B. Chronic stricture, secondary type, previous inguinal adenopathy	6	42	6	..	1 yr.	Frei antigen	4	30 wks.	26	..	2	2		
						Dilatation	1	30 wks.	1		
						Tannic acid	1	30 wks.	1	..	2	1
						Tartar emetic	1	30 wks.	1		
						Operative	1	30 wks.	1	..		
C. Acute proctitis, secondary type, previous inguinal adenopathy	2	49	2	..	8 mos.	Frei antigen	2	64 wks.	23	2		
						Fuadin	1	1		
D. Ulcerative sigmoiditis	2	39	2	..	1½ yrs.	Tartar emetic	1							
						Emetine } Carbarsone }	1	4 wks.	2	1	1
E. Condyloma, fistulas in ano	1	33	1 yr.	Incision	1	3 wks.	1		

TABLE 6.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 32 FEMALES WITH RECTAL LESIONS.

Classification.	No. of cases.	Average age.	Type.		Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Result.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
			Tub.	Dia.					Excellent.	Good.	Poor.			
A. Rectal stricture	17	30	8	9	3 yrs.	Frei antigen	2	20	2			
						Resection	2	1	1*			
						Non-sp. prot.	1	1			
						Colostomy-dil.	2	2 yrs.	2	4	1	
						Dilatation	2	2	..			
						Operative	2	2			
						None	5	5			
						Tartar emetic	1	1			
B. Rectal stricture with rectovaginal fistulas	5	36	2	3	10 yrs.	Non-sp. prot.	1	8 wks.	1			
						Dilatation	1	12 yrs.	1			
						Frei antigen	1	8 wks.	16	..	1	1	1	
						None	2	2 yrs.	1*	1†		
C. Rectal stricture, pelvic exudate	1	34	..	1	Unkn.	Röntgen ray	1	1				
D. Rectal stricture, inguinal adenopathy	2	29	1	1	3 yrs.	Dilatation	2	Unkn.	1	1		
E. Acute and chronic proctitis	1	26	1	..	9 yrs.	Frei antigen	1	40 wks.	24	1	1	
F. Peri-anal excoriations	2	27	5 mos.	Frei antigen	2	12 wks.	13	..	2	2		
G. Fistulas in ano	3	23	6 mos.	Frei antigen	3	Unkn.						
H. Rectal stricture, primary infection	1	11	1	..	4 yrs.	Frei antigen	1	2 yrs.	40	1		

* Fatal.

† Poor.

The tabulation of the type of treatment and results obtained shows the comparative efficacy of the procedures used thus far. The totals for the group show good results in 17 and poor results in 38 cases. Surprisingly enough, no cases could be considered completely healed. The reason for this will become more evident when all procedures used are considered separately (Table C).

TABLE C.—RECTAL CASES—MALE 23 AND FEMALE 32—TOTAL 55.

Type of treatment.	No. of cases.	Duration of disease (yrs.).	Duration of treatment.	No. of injections.	Results.		
					Healed.	Good.	Poor.
Frei antigen	25	4	1 yr.	23	..	7	18
Non-specific protein therapy .	2	3	1 yr.	2
Tartar emetic	5	4	7 mos.	5
Roentgen ray therapy . . .	1	4	3 wks.	1
Dilatation	9	5	1 yr.	8	1
Colostomy and dilatation .	2	6	1 yr.	2	
Mobilization of rectum with excision of scar	3	3	4 yrs.	3
Resection	2	3	2 yrs.	2
Incision of fistulas	1	1	3 wks.	1
No treatment	5	4	3 yrs.	5

The intravenous use of Frei antigen alone has yielded surprisingly good symptomatic relief. The patients lose their constitutional symptoms and lose most of their rectal pain. This occurs as early as after the second injection. The disease process, however, appears for the most part anatomically unchanged. It must be observed that the treatment is continued over a period of many months or years. For a variable period (2 to 3 months) after the administration of Frei antigen no appreciable change will be seen. However, after this period evidence of slow regression will become apparent. Epithelization of ulcerated surfaces, beginning fibrosis and a subsidence of the acute and chronic inflammation will now ensue. In the group so treated there was certainly no progression of the disease process. It is the writer's impression that the effect of the antigen is definitely beneficial, even if not curative. The good results obtained are thus mainly functional and not anatomic. When administered to patients having fibrotic changes, the Frei antigen shows no evident effect. The fibrosis represents an end stage of the local process, and therefore is not likely to be affected by the antigen. It must be remembered, however, that acute and subacute pathologic lesions have been demonstrated in the pelvic lymph nodes in cases of fibrous stricture as long as 12 years after the onset of the lesion. It would seem advisable, therefore, that even these cases be given Frei antigen in an effort to cause these foci to subside. A course of at least 6 weeks' treatment similar to the treatment for inguinal bubo seems advisable before mechanical measures are resorted to.

The use of tartar emetic, Roentgen rays and non-specific protein therapy have all proved of no avail.

Rectal dilatation alone was found of definite benefit in those cases where actual disease had completely subsided. A surprisingly small lumen will leave the patient asymptomatic. Dilatation alone is contraindicated in the presence of active proctitis or pelvic inflammation. It is associated with severe local pain and marked systemic reactions. Mathewson¹² particularly recommends dilatation. He believes colostomy need not be resorted to, since 87 of his 89 cases with obstructive stenosis were relieved by dilatation alone. In the writer's series, dilatation alone was extremely effectual when the above-mentioned indications presented themselves. Of 9 cases, 8 yielded good functional results.

Colostomy may, at times, become an emergency procedure. In case of partial obstruction, colostomy may be optional. However, colostomy may be delayed or possibly avoided by the use of intestinal intubation for abdominal decompression described by Abbott and Johnston.¹ After the distention is relieved, sufficient time may be taken for a thorough investigation of the case and the most suitable course followed. As a rule, colostomy should be seriously considered in cases with fulminating lesions which do not react to palliative measures or to attempts at immunization with Frei antigen. Cleansing of the distal loop and rest have proved very useful and permitted a later closure in some cases. The suggestion of Lockhart-Mummery for the treatment of fibrous stricture of the rectum may well be followed as a general principle. "To ascertain the type and extent of the stricture, it is advisable to examine even with partial dilation, so that the upper limits can be explored and the condition of the proximal bowel immediately above verified. Sigmoidoscopy may thus be performed under anesthesia if necessary. This should be done with great care, and splitting of the rectal wall when inflammation is present should be avoided. In suitable cases the stricture is dilated and treated by continual cleansing. Results of subsequent dilatation are excellent and permanent, if the patient will endure the inconvenience of dilating long enough to counteract the contraction of scar tissue."

Hayes,⁸ reporting 160 cases of rectal stricture, found colostomy a necessary procedure in 31 cases. When these cases were followed up, he found it possible to close the colostomy in only one of the operated cases. He was undoubtedly dealing with the tubular proliferative type of rectal stricture.

Colostomy and dilatation thus play an important rôle in the treatment. The surgical risk is very small as compared with the following procedures recommended by other authors.

Mobilization of the Rectum and Excision of the Perirectal Scar Tissue. This procedure wherever done was attended with a failure

and recurrence. It results in stirring up of latent foci in the endopelvic fascia and eventually produces more fibrosis, creating a condition much worse than that for which the procedure was undertaken. The object of the operation is to release the supposedly disease-free rectal wall. Since the rectal wall itself is always involved, the rationale for the procedure is faulty. Good results were reported in 2 cases by Gomez-Duran⁶ with this procedure upon old healed strictures of the ring type. However, in this type of lesion the procedure is unnecessary, since dilatation alone is sufficient.

Resection of the Rectum. A review of the procedure of radical resection for lymphogranuloma venereum shows a series of disastrous and unsatisfactory results from every point of view. Thus, Frei^{1b} reviewed 105 cases of various types of rectal amputations with a follow-up of 90% unsuccessful results.

Peterson¹³ quotes Anschuetz as having a mortality rate of 39% among 13 cases resected. The remaining cases showed poor follow-up results. Only those with colostomies did comparatively well. Radice¹⁵ likewise reported 16 cases with 7 resections with poor results. The resulting complications of perineal fistulas, rectovaginal fistulas and permanent incontinence were attributable to persistence of a low grade infection. The reasons for failure are evident when the procedure is attempted. The mobilization of the diseased rectum is extremely difficult. The normal anatomic planes of cleavage are entirely obliterated and replaced by inflammatory scar tissue. The mesosigmoid likewise becomes shortened by the extension of the inflammation from below. This most often prevents an adequate mobilization for use in anastomosis. Preservation of the sphincter ani is a practical impossibility in most cases because the perianal tissue is most often itself involved.

A very important consideration that accounts for the failure and high mortality in resection is the fact that as long as there remains any evidence of activity of the disease one must assume that a phlegmonous type of inflammation is still present in the endopelvic fascia. Attempt at dissection in such tissue is analogous to incision of a phlegmon elsewhere and there is a definite risk of a lymphatic spread of the disease.

Incision or Excision of Fistulous Tracts. The repair of rectovaginal fistulas or excision of rectal fistulas has proved unsatisfactory as long as any disease remained active in the rectum itself. Recurrences have resulted invariably.³ Before this type of surgery is attempted the disease process itself must be cleared up more or less completely.

Palliative Procedures. Palliative methods such as rest in bed, low-residue, high-vitamin diet, retention enemata of olive oil or cotton seed oil, rectal irrigations with 2% tannic acid, and solutions of quinine bisulphate, 1 : 4000, have been used with benefit to the patient.

From the foregoing one may reasonably conclude that radical surgical procedures alone or palliative methods alone are inadequate. A rational combination of both palliative procedures and the more conservative surgical methods seems the most advisable course to take at present in the treatment of the rectal lesions.

CASES WITH PERSISTENT GENITAL LESIONS. A total of 59 cases of this type were observed, 26 females and 33 males. The average duration of the lesions was over 2 years. Among the females, the lesions ranged from periurethral granulomata with esthiomene to the various ulcerations of the genitalia or their resulting fibrosis (Table 7). In the males, the lesions were represented by chronic ulcerations of the penis (Table 8).

TABLE 7.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 26 FEMALES WITH GENITAL LESIONS.

Classification.	No. of cases.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treatment.	Aver. No. of inj.	Result.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
							Excellent.	Good.	Poor.			
A. Periurethral granuloma with esthiomene	7	28	3 yrs.	Frei antigen Tartar emetic	7 1	8 mos.	32	2	3	..	3	
B. Ulcerations of labia minora with esthiomene	5	28	2 yrs.	Frei antigen	5	8 mos.	33	2	..	1	4	
C. Stenosis of vaginal introitus	3	32	1½ yrs.	Frei antigen	3	6 mos.	29	..	3	..	2	
D. Fourchette: chronic ulceration	3	32	1½ yrs.	Frei antigen	3	5 mos.	10	3	2	
E. Chronic cervical erosion	2	36	Unkn.	None	2			
F. Ulceration of perineum	1	36	Unkn.	Frei antigen	1	1 wk.	3	1	1	
G. Chronic hypertrophic ulceration of vulva	1	36	9 yrs.	Frei antigen	1	4 wks.	22	1		
H. Ulceration of vaginal wall	1	24	Unkn.	None	1		
I. Esthiomene	1	27	2 yrs.	Frei antigen	1	5 mos.	22	1		
J. Esthiomene with recto-vaginal fistula	1	26	3 wks.	None	1			

Treatment with Frei antigen alone was effectual in 24 of 39 cases (60%). Other methods such as tartar emetic, cauterization, or operative measures, yielded good results in 2 out of 7 cases (28%). In 13 cases no treatment was used and poor results were uniform. The lesions progressed.

The largest single subdivision among the females is that of periurethral granulomata with esthiomene (12 cases). These periurethral lesions lead to obstruction of the urinary flow and thus produce uremic symptoms and predispose to infection of the entire urinary tract. Local palliative measures and bladder decompression become urgent procedures for immediate relief. Although the lesions grouped

under the heading of esthiomene represent swellings due to edema, a good deal of the deforming swollen lesions are made up of fibrous tissue. Healing of local ulcerations may reduce the edema present

TABLE 8.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 33 MALES WITH GENITAL LESIONS.

Classification.	No. of cases.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Results.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
							Excellent.	Good.	Poor.			
A. Erosion corona glans penis (small)	12	38	14 wks.	Frei antigen 6 Tartar emetic 1 None 6	11 wks.	8	6	9	3	4
B. Ulceration glans, lymph-chancere	10	34	9 mos.	Frei antigen 5 Tartar emetic 2 Operative 2 None 1	26 wks.	24	1	1	3	7	4	1
C. Paraphimosis lymph-edema	2	28	2½ mos.	Frei antigen 2	22 dys.	8	..	1	1	1	2	
D. Herpes glans	2	30	2 wks.	Frei antigen 2	4 wks.	7	2					
E. Chronic ulcer shaft	1	31	1 mo.	None								
F. Multiple ulcerations glans	1	31	1 mo.	None								
G. Bubonulus shaft	1	26	3 wks.	Frei antigen 1	2 mos.	21	1					
H. Urethral fistula perineum	1	54	20 yrs.	Frei antigen 1	4 mos.	32	1			
I. Urethritis	3	24	4 wks.	Frei antigen 3	4 wks.	6	3					

but will invariably leave the thickening due to fibrosis entirely unaffected. Thus, one must be content with the healing of open ulcerations and eventually resort to surgical removal of obstructing or deforming lesions. Operative procedures are contraindicated in the presence or even suspicion of the presence of an inflammatory focus.

Discussion. An analysis of all forms of treatment used in this group of 300 cases reveals the following (Table 9):

Approximately 33% of the cases seen, heal spontaneously without any treatment. These cases were observed among the glandular group, which represents the mildest form of this disease. No spontaneous cures were seen among the two other groups.

When any method of local treatment is used about 46% of the cases have good results when the treatment is carried out over a period of at least 7 or 8 months. In the rectal cases treated by dilatation alone, the good results may be attributed to the fact that the disease process had already spent itself when the treatment was begun.

The best results were obtained by the use of Frei antigen intra-

venously in the manner described (82%). The best results were obtained in the glandular group, although the symptomatic and systemic relief in the rectal and genital cases deserves mention. Although no complete cure was obtained in the rectal group by the use of Frei antigen alone, the disease did not progress after this form of treatment was instituted.

TABLE 9.—LYMPHOGRANULOMA VENEREUM. RESULTS OF TREATMENT.

		Glandular.	Rectal.	Genital.	Total.
Frei antigen	Healed	119	0	16	135 (67%)
	Good	17	7	8	32 (15%)
	Poor	7	18	15	40 (18%)
	Total	143	25	39	207 (100%)
Other methods of treatment	Healed	2	0	1	3 (5%)
	Good	12	10	1	23 (41%)
	Poor	10	15	5	30 (54%)
	Total	24	25	7	56 (100%)
No treatment	Healed	4	0	0	4 (11%)
	Good	8	0	0	8 (22%)
	Poor	7	5	13	25 (67%)
	Total	19	5	13	37 (100%)
Total		186	55	59	300

Summary and Conclusions. 1. The results of treatment of 300 cases of lymphogranuloma venereum are reported.

2. Two hundred and seven cases were treated by means of Frei antigen intravenously. Local palliative and radical surgical measures were used in the remaining 93 cases.

3. A uniform routine for the intravenous administration of Frei antigen is suggested. The patients receive 0.3 cc. of infiltrated antigen, the same as that used for skin testing, on alternate days.

4. Various types of reactions to the initial intravenous injection are described. No alarming untoward reactions were observed in any case.

5. The rationale for the therapy of lymphogranuloma is based upon the fact that this disease is systematic in nature, even though its localized manifestations are mainly lesions in the pelvic region.

6. All of the localized manifestations of the disease are the results of inflammation in any of its stages and range from acute exudative processes to the final chronic proliferative or fibrotic conditions of the various structures affected.

7. Surgical treatment alone or palliative treatment alone have proved inadequate for the complete cure of this disease.

8. Surgical intervention is indicated only after all local evidence of any inflammation has subsided.

9. In general, the most useful local procedures in all the lesions

seen in lymphogranuloma are conservative ones, in combination with Frei antigen intravenously.

10. For the inguinal adenopathies, aspiration of inguinal abscesses where necessary and intravenous Frei antigen have been found sufficient for treatment.

11. For the rectal lesions, temporary or permanent colostomy as indicated and dilatation where possible, in combination with local palliative and systemic Frei antigen intravenously, are advised.

12. Intravenous Frei antigen was found to be the most useful single method of therapy.

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A CASE OF FATAL SUBACUTE MYOCARDITIS OF UNKNOWN ETIOLOGY.

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THE case presented in this paper is that of a middle-aged woman who died suddenly following the subtotal excision of a simple colloid goiter. It is of interest because the only significant finding at autopsy was a most unusual type of myocarditis. It is thought to be worthy of report because it is impossible to assign the responsibility for the myocardial damage to any of the known causes of myocarditis.

Case History. The patient, a woman of 50, had worked in a tuberculosis sanatorium for approximately 30 years, at first as a nurse and later as a laboratory technician. She was under constant medical supervision for this period. The history which follows was obtained through the kindness of Dr. C. D. Parfitt, Loomis Sanatorium, Loomis, N. Y.

As far as is known, the patient was never known to have had rheumatic fever or any other serious illness until 1907, when at 20 years she experienced several small hemoptyses. She entered a sanatorium, where tubercle bacilli were found in her sputum. With adequate treatment her condition improved and eventually she was able to take training as a nurse. She nursed in one sanatorium uninterruptedly until 1916 when she obtained a position as laboratory technician at another sanatorium.

In 1925, a hysterectomy for myomata was followed by a pelvic abscess which drained for 3 weeks. Her recovery was otherwise uninterrupted, she gained weight, resumed work and lived a regular, fairly active life until 4 months later, when she suffered another small hemoptysis, unaccompanied, however, by cough or sputum. After 9 weeks in bed she returned to work. Five years later, in 1930, she again coughed up a small amount of blood, but examination of the chest revealed only a very slight residual lesion at the apex of the right lung and a somewhat more diffuse involvement on the left side above the third rib.

During the year before her death the patient was, to all appearances, in excellent health and her exercise tolerance was good. From time to time she complained of a sensation of fullness in the throat. She had had a small goiter for years, but there were no symptoms of hyperthyroidism. In September, 1937, as the goiter appeared to be increasing in size, a subtotal thyroidectomy was performed. Physical examination before operation revealed a normal cardiovascular system. Electrocardiograms were not taken. The temperature was normal and the pulse rate not elevated. The patient's postoperative condition was satisfactory and she was given only a moderate amount of sedative drugs. Eighteen hours after operation her breathing became irregular, she gasped a few times and died suddenly.

Autopsy. Autopsy (A-321-37) included examination of the thoracic and abdominal organs, the brain and the spinal cord. The neck organs were not removed except for remnants of thyroid tissue, but were examined thoroughly *in situ*. The findings of interest were as follows:

The body was that of a well-nourished but not obese woman. At the base of the neck anteriorly was a recent collar incision. The tissues in this region were infiltrated with dark, jelly-like blood clot, and a small amount of blood had tracked down through the superior mediastinum into the layers of the pericardial sac, and laterally on either side under the layers of the pulmonary ligaments to the mediastinal surfaces of both lungs. There was a small nodule of thyroid tissue on the right side, weighing 12 gm. and a similar nodule on the left side weighing 6 gm. Fibrous adhesions were present at the apex of the left lung and a small, firm nodule was felt in this region which on section proved to be a grayish, fibrous scar from which fibrous strands radiated into the surrounding lung tissue. Fibrous adhesions covered the antero-lateral surfaces of the right lung and at the base was a pale purplish area of superficial collapse.

The heart weighed 295 gm. It was normal on external examination. The endocardial surfaces were smooth and glistening. The valve leaflets were thin and pliable, except along the free borders of the mitral valve where there was some slight whitish, fibrous, nodular thickening. The coronary arteries were freely patent and showed only very slight sclerosis. The cut surface of the myocardium was pale brownish with a few barely distinguishable small, white, fibrous flecks in the left ventricular wall near the base.

The sigmoid colon was the site of many diverticula. The uterus had been removed at a long-previous operation. All the other organs were essentially normal. No obvious cause of sudden death could be found.

Microscopic Examination. Several sections from the anterior wall of the left ventricle and the interventricular septum were stained with hematoxylin-eosin and various special stains. They showed numerous focal lesions of various sizes, some of which were perivascular but mostly not related to blood-vessels (Fig. 1). The myocardial fibers in such places had disappeared leaving elongated patches of irregular outline infiltrated with lymphocytes. Macrophages and plasma cells were present in smaller numbers and there were occasional neutrophils. Around the boundaries

of these areas were fragments of necrotic muscle; some were multinucleated, with their pyknotic nuclei scattered throughout the cytoplasm in a haphazard fashion, while other fragments were pale and completely anuclear. There were also in each focus several large, oval cells whose many nuclei were distributed around the periphery at one pole, giving them a striking resemblance to typical Langhans giant cells (Fig. 2). These were histologically similar to, if not identical with, true foreign body giant cells. The plump oval nuclei of young proliferating fibroblasts were also present. All these elements were disposed on a pinkish, thready, fibrillar, connective tissue background, composed in part of the remnants of the sarcolemma sheaths of the necrotic muscle and in part of newly formed connective tissue.

The muscle fibers between the focal lesions showed some loss of their cross-striations and some nuclear swelling. In several situations the fibers were spread apart as if by edema fluid, and here and there loosely arranged lines of lymphocytes and macrophages lay between them. The coronary vessels within the myocardium showed no significant inflammatory or degenerative change. In a few there were small, spurlike projections of the intimal coat which were made up of pale eosinophilic, subendothelial, granular material. Sections (Levaditi and Ziehl-Neelsen methods) showed no spirochetes or acid-fast bacilli. A search for other microorganisms was carried out on sections stained by the Gram method but no bacteria were found.

Microscopic examination of the thyroid tissue removed at operation, as well as that which remained at autopsy, showed encapsulated nodules composed of acini containing much colloid and lined by flattened, epithelial cells. Some nodules had undergone cystic degeneration in their central portions. In none of the sections was there any evidence of hyperplasia.

Examination of microscopic sections of the liver revealed small, pale areas of recent focal necrosis without evidences of inflammatory reaction. Sections of the brain revealed a small amount of patchy gliosis surrounding an area of old focal necrosis measuring approximately 1 mm. in diameter in the head of the right caudate nucleus. Sections of other organs showed nothing of significance with relation to the myocarditis.

Discussion. It is reasonable to suppose that this patient died as a result of the widespread myocardial lesions which have been described; clinical evidence of postoperative shock or laryngeal obstruction was lacking and a complete postmortem examination failed to reveal any of the usual causes of sudden death. The minute area of necrosis in the caudate nucleus was of very long standing, as evidenced by the surrounding gliosis and could not be related to the patient's sudden death. The focal necrosis of the liver was of recent origin. What relation, if any, either of these lesions bears to the myocarditis is not clear. It is evident that the myocarditis was of an unusual type. The patient was under competent medical supervision for 30 years previous to her death and during that period no sign of cardiac disease was manifested, and there was no indication of any condition which might have been etiologically related to the myocarditis. There was nothing in the history nor in the autopsy findings to suggest that an acute, infectious disease was the cause of the myocardial damage. The absence of pericardial and endocardial involvement as well as the histologic

FIG. 1.

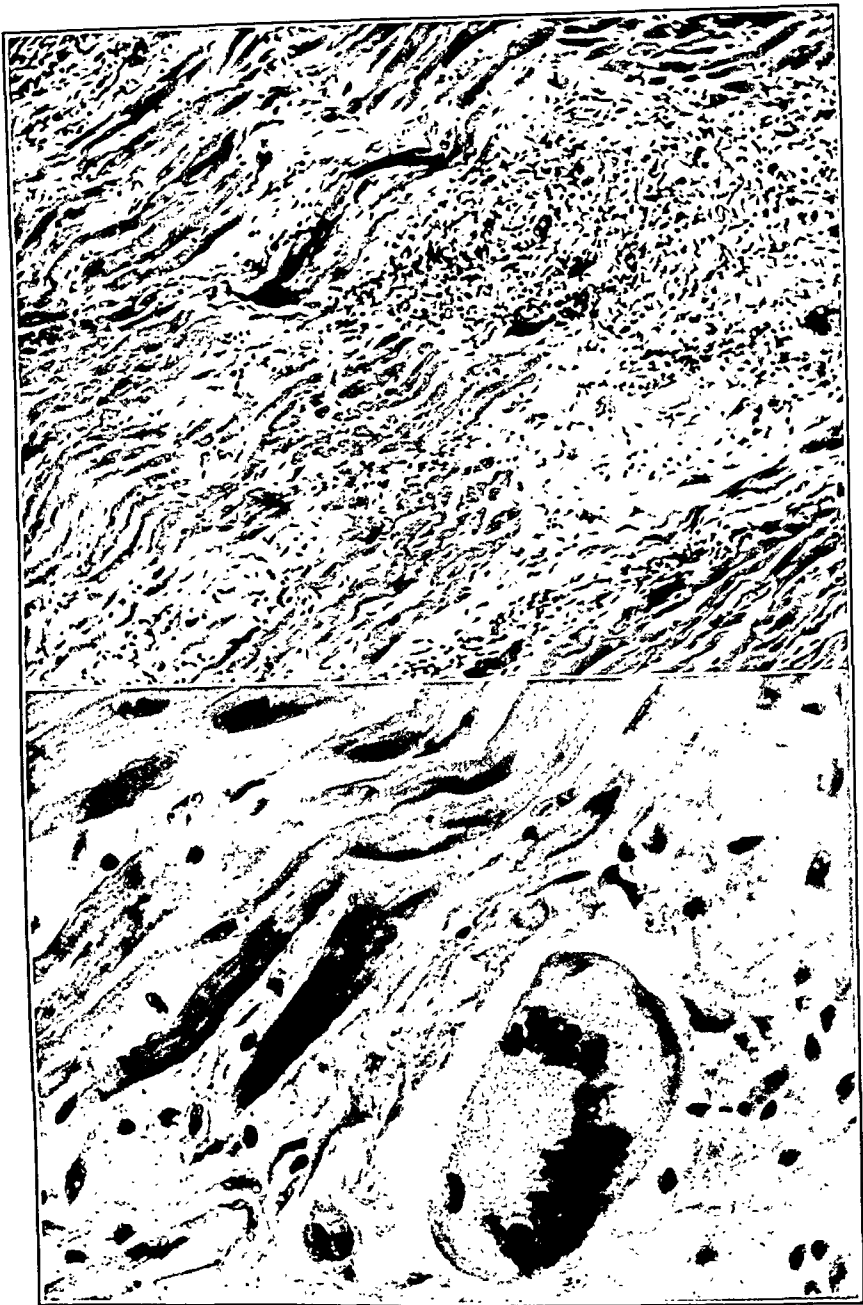


FIG. 2.

FIG. 1.—Section of the heart. An elongated patch is seen in which myocardial fibers have disappeared and are replaced by lymphocytes, macrophages, plasma cells and proliferating fibroblasts. There are also fragments of necrotic muscle, some of which are multinucleated. Hematoxylin-eosin, $\times 100$.

FIG. 2.—Section of the heart under high magnification. There is a large oval giant cell with peripherally distributed nuclei, resembling a typical Langhans giant cell. Hematoxylin-eosin, $\times 400$.

appearance of the myocardial lesions precluded a diagnosis of rheumatic myocarditis. The state of the coronary vessels and the widespread focal distribution of the lesions showed that the condition was not ischemic in nature. It is necessary, therefore, to consider the rarer causes of inflammatory changes in the myocardium.

In 1916, Fahr³ described the finding of fragmentation and dissolution of the cardiac muscle fibers with round-cell infiltration and fibrosis in persons with goiter. Since that time the association of myocarditis and goiter has been reported in only a small number of cases.^{7,9,12,18} In all such cases, however, the myocardial change was found to be associated with severe hyperthyroidism, but in the present case the patient's goiter was both symptomatically and histologically non-toxic. It seems reasonable, therefore, to conclude that the cardiac lesions were not due to it.

Hutchinson-Boeck's disease,^{10,13} which is known by a variety of names, including sarcoidosis, lupus pernio and benign lymphogranulomatosis, is a condition characterized by the development of chronic granulomatous lesions usually confined to the skin and lymph nodes but often widely disseminated through the body and even involving the heart. It is believed by many to be a tuberculous manifestation; the lesions are rare in the heart and in none of the cases reported was the heart alone involved. The cardiac lesions in the present case lacked the epithelioid-cell proliferation characteristic of Hutchinson-Boeck's disease and presented a marked inflammatory reaction as well as evidences of necrosis, neither of which is found in this condition. For these reasons a diagnosis of Hutchinson-Boeck's disease could not be supported.

Syphilitic myocarditis, according to Warthin,^{17a,b} is characterized by degenerative changes in the muscle fibers with a subacute infiltration of lymphocytes and plasma cells between the fibers. In some acute cases, monocytes and neutrophils are seen. In a case reported by Hamman and Rich⁸ there was actual necrosis of the muscle fibers. The occurrence of a syphilitic arteritis of the larger coronary vessels and an "endoperiarteritis" of the smaller branches is stressed by Warthin, Vaquez¹⁶ and others. In the present case, no such vascular lesions were found. Serologic tests for syphilis were not done but as the lesions were focal in distribution, as no spirochetes were found in sections stained by the Levaditi method, as there was an absence of syphilitic lesions elsewhere in the body and as there was no history of syphilis, one must conclude that a syphilitic origin for the condition is most unlikely.

At the time of her death this patient had a healed tuberculous lesion at the apex of the left lung and her history showed that she had suffered from hemoptysis several times in the past, the most recent occasion being 8 years before death. The possibility of a

tuberculous origin of the myocarditis must therefore be considered, though tuberculous myocarditis is extremely rare in man. If a tuberculous infection is to reach the myocardium it is apparent that it must do so either by extension through the pericardium, or by hematogeneous spread from a distant focus. The autopsy findings are against both possibilities in this case. No mediastinal tuberculosis was present, and the only possible extracardiac focus of infection, that at the apex of the left lung, appeared to be definitely healed. Furthermore, if hematogeneous dissemination of tubercle bacilli had occurred, one would expect to find tuberculous lesions in other organs but in this case no such lesions were found. The histologic appearance of the lesions, also, did not support a diagnosis of tuberculous disease: there was no evidence of caseation and no epithelioid-cell proliferation; some of the giant cells were very similar to those of tuberculosis, but can be regarded equally well as having been formed in response to the stimulus of an irritant of non-tuberculous nature.

Under the name of subacute interstitial myocarditis several French investigators have described a condition which they believe to be an atypical form of tuberculous disease. The case of Gallavardin and Gravier⁵ was that of a man of 33 who died of rapidly progressive heart failure. Autopsy revealed tuberculous peritonitis and a healed tuberculous process at the apex of one lung. Microscopic examination of the heart showed small islands where the muscle fibers were fragmented and decolorized with elsewhere large areas of interstitial involvement in the form of dense fibrosis with a few inflammatory cells. The authors reported the case as one of subacute interstitial myocarditis probably of tuberculous origin, but emphasized the non-specific histologic character of the lesion.

This case of Gallavardin and Gravier has many points of similarity to others of still more obscure nature. In 1899, Fiedler⁴ reported 4 cases under the title of subacute interstitial myocarditis. The clinical picture was one of rapidly progressive heart failure and autopsy showed a diffuse interstitial cellular infiltration of the myocardium. Since that time somewhat similar conditions have been described under such titles as "isolated myocarditis," "idiopathic myocarditis," "primary myocarditis," and "Fiedler's myocarditis." In the majority of such cases the heart was hypertrophied, the chambers dilated and the organ flabby. There was no pericardial change and the valves were normal. Mural thrombi secondary to the myocardial lesions were not rare. The cut surface of the heart muscle in some cases showed grayish streaks and flecks while in others it appeared normal. Microscopic examination showed a diffuse infiltration of the interstitial tissue by lymphocytes, plasma cells and macrophages. Some authors reported a predominance of eosinophils. Young fibroblasts and areas of

fibrosis were seen. In some cases there were minimal degenerative changes in the muscle while in others there was necrosis of fibers. Bailey and Andersen,² in a review of the literature on this subject, noted the description of multinucleated fragments of muscle cells. de La Chapelle and Graef¹¹ mention the description in Saltykow's case of "cells thought to be degenerating forms of muscle cells . . . which are also found forming giant cells." The majority of investigators, however, regarded the primary change as interstitial.

In these cases there was no evidence that the myocardial damage was due to any of the usual causes. A history of rheumatic fever or other infectious disease could not be obtained, and the coronary arteries showed no significant arteriosclerotic narrowing. An infectious or toxic etiology was suggested by Aschoff,¹ and von Gierke⁶ believed the lesion in his case to be a syphilitic manifestation. Bailey and Andersen² have been impressed with the frequency of the report of an antecedent or coëxisting infection such as a carbuncle, an infected burn or acute gonorrheal urethritis. Other authors regarded the cases they reported as having a specific but undetermined etiology.

Scott and Saphir,¹⁵ in 1929, collected 30 of these obscure cases from the literature and added 2 of their own. It would appear that they regarded such cases as representing a pathologic entity. In the writer's opinion, this concept is not warranted. The only factors common to all are rapidly progressive myocardial failure or sudden death and an acute or subacute inflammation of the myocardium in the absence of any known cause of myocardial damage. The attribute of obscurity cannot be considered as a justification for grouping these conditions together as manifestations of a single disease. It appears probable that the group is a heterogeneous one, including atypical varieties of tuberculous, syphilitic and rheumatic myocarditis as well as certain other inflammatory conditions of unknown and probably variable causation. This case, therefore, is presented as one of subacute inflammation of the myocardium of unknown etiology. It is of interest to note in this connection that Rich,¹⁴ who examined sections of the heart from the case under discussion, stated that he had seen 6 others precisely similar, in which there was no constant association with active tuberculosis, syphilis or rheumatic fever.*

Summary. A case is presented in which sudden death after subtotal excision of a simple colloid goiter was found to have been associated with myocarditis of an unusual type. Microscopic examination of the myocardium revealed many small foci of subacute inflammation in which muscle fibers had disappeared. Giant

* Since this paper was submitted for publication, Jonas (Bull. Johns Hopkins Hosp., 64, 45, 1939) has reported 5 cases of "granulomatous myocarditis." These were presumably included in those referred to by Rich.

cells were prominent among the mononuclear inflammatory cells and proliferating fibroblasts in these areas.

The origin of the cardiac lesions is discussed and it is concluded that they were not related to the patient's goiter and did not seem to be due to tuberculosis, syphilis, rheumatic fever or Hutchinson-Boeck's disease. The case is presented as one of subacute myocarditis of obscure etiology.

My thanks are due to Dr. G. Lyman Duff for his assistance in the preparation of this paper.

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PROGNOSIS IN DIABETIC COMA: BASIC IMPORTANCE OF MENTAL STATE.

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ANY one who has much to do with diabetic coma soon comes to realize that even the best therapy remains highly unsatisfactory in the majority of unconscious cases. Practically no therapeutic progress has been made in this field since the early days of insulin, nor are we any nearer the answer as to why the unconsciousness of diabetic ketosis regularly carries such a high fatality rate. From the findings presented in subsequent paragraphs it would seem that by far the most important factors in coma prognosis, even with the best of treatment, are the depth of the stupor and its duration before treatment is instituted. The duration of acidosis (without complete

unconsciousness) seems to be of minor importance, but, once central nervous system damage has produced the unconscious state, chances for reversal of this damage seem to diminish rapidly. Nor does elimination or improvement of the ketosis offer any great assurance of recovery. The amounts of insulin, glucose, and alkalies administered seem within reasonable limits to affect the prognosis much less than do the depth and preceding duration of the stupor.

In order to gain a clearer picture of the prognosis and factors behind the high coma mortality, a careful analysis was made of the clinical records of all diabetic ketosis and coma cases admitted to the Cincinnati General Hospital for the 15 years from 1923 to 1937. Facts taken from the records included age, sex, color, duration of acidosis before admission, mental state on admission, blood and urine sugar determination, blood alkali reserve, complications on admission and after admission, treatment with insulin, glucose and alkalies, and outcome and autopsy. Various groupings of the cases were made in order to test for significant relationships and the relative importance of the different factors. From all the 15 years' records only 92 cases were found which satisfied clinical and laboratory requirements for impending or actual coma. Those with mild acidosis, without significant mental symptoms, were not included since adequate and satisfactory methods of treatment are already available and in general use.

The duration of the ketosis was reckoned from that point at which persistent vomiting and drowsiness began. As the ketosis progressed, certain mental states developed by which the patients were classified as: 1, *conscious*, those who were drowsy but could answer questions and take fluids by mouth; 2, *semi-conscious*, those who responded to peripheral stimulation but were unable to answer questions or take fluids by mouth, and, 3, the *completely unconscious*, those who did not respond to any stimulation.

Of the total 92 cases studied, 51 were white and 41 colored. The white patients, 28 of whom died, presented a mortality of 54.9%, while 19 (46.3%) of the colored died. In the out-patient dispensary and diabetic clinic for ambulatory cases, white patients outnumber the colored 2 to 1, while with the diabetic coma admissions the proportion is only 5 to 4. Whether this represents a greater severity of the disease among the colored or only greater neglect in handling cannot be said. It is of interest, however, to note the greater severity of the disease in northern colored reported by Mills,⁶ who found the diabetic death rate actually higher among colored than white in the north. Joslin⁵ also found the disease increasing more rapidly in the colored than in white.

There were 28 males and 64 females. Of the males, 20 were white and 8 colored. Of the females, 31 were white and 33 colored. Eight of the 28 males died (28.5%). In the female group of 64

there were 39 deaths (60.9%). The preponderance of female cases and deaths is unusually striking. Several years ago it was thought that males were more predisposed to diabetes than females, but in recent years the reverse has been shown to be true.⁵ Attending the out-patient diabetic clinic in 1937, the ratio of males to females was 1 to 1.7, while in the coma group the ratio was 1 to 2.3. In the out-patient clinic group the ratio of white males to females was 1:1.37, while with the colored it was 1:2.72.

In an analysis of the cases according to age groups, another very striking sex factor is found. Ketosis and coma in females seem particularly prone to occur during puberty and at the menopause, and at those times to be more highly fatal. Table 1 brings out this fact rather clearly. In the 40-49 year age group there were 16 females of whom 13 died (81.2%). Of the 5 male patients in this age group all recovered. Puberty in the male brings a heightened incidence of coma, but in boys of the 10-19 year age group 8 out of 9 cases recovered, while with the girls 6 out of 11 died. These findings fit in well with the known fact that disturbances in other endocrine glands bring greater severity and frequency of diabetes.

TABLE 1.—COMA AND PRE-COMA CASES CLASSIFIED BY SEX, AGE, AND OUTCOME.

Age group (years).	Males.		Females.		Mortality. %
	Recovered.	Died.	Recovered.	Died.	
0-9	2	1	0	0	
10-19	8	1	5	6	55
20-29	1	0	8	4	33
30-39	1	1	5	5	50
40-49	5	0	3	13	81.2
50-59	2	3	3	5	62.5
60+	0	2	3	6	67

TABLE 2.—MENTAL STATE, AGE, MORTALITY, AND DURATION OF KETOSIS SYMPTOMS PRECEDING HOSPITAL ADMISSION.

	Duration (in hours) of mental symptoms preceding hospitalization.			
	Conscious and semi-conscious group.		Unconscious group.	
Age group. (years).	Recovered.	Died.	Recovered.	Died.
0-9	?-12	10		
10-19	1-2-10-20-14-18-10-18	5	20-12	24-36-6-15-?-18
20-29	10-18-12-12-36-12-24-36		12-16	15-?-10-8-15
30-39	?-12-?-8	20-24	15-10	15-18-24-9
40-49	?-10-?-8-24	24-?-12-12	12-16-12-6	?-16-18-16-12-48-36
50-59	12-8-8-24	?	12-8	17-?-36-14-12-18
60+	18	18	10	8-12-?-?-?-?-15
	Aver. = 14.9 hrs.	Aver. = 15.6 hrs.	Aver. = 11.9 hrs.	Aver. = 18.5 hrs.
Average mortality		Average mortality		
Under 40 years = 14.4%		Under 40 years = 71.4%		
40 years and over = 35.3%		40 years and over = 75%		

(?)—Duration of ketosis unknown. Other numbers represent hours in ketosis preceding hospital admission.

In Table 2 is presented evidence of the great importance which attaches to the degree of central nervous system damage brought on by ketosis. Duration of the ketosis is shown for the individual

cases, with grouping according to mental state on admission and whether death or recovery ensued. Of the 92 cases, 49 were completely unconscious on admission, with an average of 16.2 hours in ketosis before admission and a mortality of 73.5%. The average duration of ketosis in the semi-conscious group of 33 was 15 hours, and the mortality 33.3%. The conscious group of 10 had been in ketosis for an average of 13 hours and included no deaths. From these findings it is evident that progressive and often irreversible changes in the central nervous system play a very important part in the prognosis of diabetic coma, for the mortality sharply increases as the patient progresses from the conscious to the unconscious state and as the ketosis continues for additional hours.

Table 3, showing further grouping of the material of Table 2, indicates still more strikingly the importance of the extent and duration of brain damage. So long as the patients are not completely unconscious on institution of proper therapy, the mortality remains low regardless of the preceding duration of the ketosis. But if complete coma has developed, even for only a few hours, prognosis

TABLE 3.—MORTALITY IN RELATION TO MENTAL INVOLVEMENT AND DURATION OF KETOSIS SYMPTOMS PRECEDING HOSPITAL ADMISSION.

Hours in ketosis before admission.	Mental state on admission.					
	Conscious and semi-conscious number of cases.			Unconscious number of cases.		
	Recovered.	Died.	% Mortality.	Recovered.	Died	% Mortality
0-8	5	1	18.2	3	4	47.3
9-14	13	3		7	5	
15-20	4	2	25.0	3	12	85.7
Over 20	0	1		0	6	

becomes much more grave. The conscious and semi-conscious patients in ketosis over 14 hours had a mortality of only 25%. But if complete unconsciousness had supervened before admission to the hospital, then a mortality rate of 47.3% was found with the 19 who had been in ketosis 14 hours or less, and an 85.7% mortality for the 21 with ketosis of longer duration. It is quite evident, then, that prognosis is largely determined by the combination of these two factors, duration of ketosis and extent of brain damage.

Let us next see what prognostic value attaches to the CO₂-combining power of the blood at the time treatment is instituted (Tables 4 and 5). For those in the conscious group, the CO₂-combining power on admission to the hospital averaged 17.1 vol. %. In those of the semi-conscious who recovered the average CO₂-combining power was 15.1 vol. %, while for those who died it was 17.7 vol. %. The unconscious group gave similar findings, with 13.2 vol. % for those who survived and 17.2 vol. % for those who succumbed. If division is made into high and low levels in an attempt to place a more exact prognostic value on the findings, no change in the results can be found. Taking only those cases with a CO₂-combining level

below 10 vol. %, we find 3 in the semi-conscious group with one death and 4 in the unconscious with only one death. And taking only those above 20 vol. % on admission, there were 4 deaths and one recovery in the semi-conscious group, and 7 deaths with one recovery in the completely unconscious. These points are strongly emphasized by the data of Tables 4 and 5 and in the summary.

TABLE 4.—BLOOD CO₂-COMBINING POWER, MENTAL STATE, AGE AND MORTALITY.

Years.	Blood CO ₂ (vol. per cent) at time of hospital admission.					
	Conscious groups.		Semi-conscious groups.		Unconscious groups.	
	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.
0-9	19		20	28		
9-19	12		16,14,19,13,12,14	10,8	18,20	8,29,16,10,11
20-29	20		12,6,14,18,21		10,5,14	14
30-39	18,17		20,19	15		25,16,10,12
40-49	21,20,20		9,14,12	28,10,21	25,8,12	28,14,16,20,10
50-59	12,12		20	22	6,14	18,13,12,22
60+						28,12,19,14, 14, 32
Aver.	17.1	—	15.1	17.7	13.2	17.2

TABLE 5.—BLOOD ALKALI RESERVE LEVEL AS A PROGNOSTIC FACTOR.

CO ₂ (Vol. %)	Mental state and percentage mortality.		
	Conscious % mortality.	Semi-conscious % mortality.	Unconscious % mortality.
20 or below	0	20	68.6
Above 20	0	80	87.5
Unknown	0	37.5	76.9
Total	0	33.3	73.5

Physicians and workers in the field of diabetes have been wont to attach great prognostic importance to the blood alkali reserve level in diabetic ketosis and coma. Some have even gone so far as to use this as the determining factor in defining and diagnosing coma for statistical purposes. Such an attitude seems entirely unjustified on the basis of our findings. In Table 4 are given the blood alkali reserve findings on admission for our whole group of 92 cases. Admission determinations were not made on every patient; but in those cases having such data, higher average values were found for those who later died than for those who recovered. Ketosis patients, either conscious or unconscious, may be admitted with CO₂-combining power below 10 vol. % and go on to recovery; or those above 20, or even 30 vol. % may go on to death if the brain damage has become too extensive or too prolonged. Little prognostic value would seem to reside, therefore, in the blood alkali reserve level.

Although the findings of Dillon and Dyer³ seem to show a higher alkali reserve in the ketosis patients who recover than in those who die, a regrouping of their data on the basis of mental state shows just the reverse to be true. Among their uncomplicated ketosis

cases were 10 unconscious patients who recovered and 27 who died. The average blood CO_2 -combining power on admission was 13.4 vol. % for those who recovered and 15.5 for those who died. These findings are in complete agreement with those of our series, showing the blood alkali reserve to be of no prognostic significance in coma cases who are unconscious on admission. Their mortality for this group was 73%—ours was 73.5%.

All the patients in our series received the generally accepted treatment. Insulin was always given in large and frequent doses. Large quantities of fluids, normal saline solution by infusion or intravenously, or water by mouth when possible, have been a routine part of treatment. The general treatment included stimulants, attention to the gastro-enteric tract, and external heat, according to the needs of the individual patients. A summary of treatment with reference to the amount of insulin given the first 2 hours and every 2 hours thereafter, and the amount of glucose and alkalis, according to mortality and mental state, is shown in Table 6. These findings show that the treatment given those who died was just as adequate as was that for those who recovered; 69 patients received an average of 110 gm. of glucose, with 31 deaths—a mortality of 45 %. Alkalis were administered to 25 patients, of whom 15 died (60%).

TABLE 6.—TREATMENT AND COMA OUTCOME.

	Conscious.		Semi-conscious.		Unconscious.	
	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.
Insulin 1st 2 hrs.	0	59 (9)	42 (12)	81 (21)	70 (35)	83 (13)
Insulin each 2 hrs.						
thereafter . . .	0	17 (9)	28 (12)	17 (20)	31 (32)	19 (13)
Glucose	0	110 (7)	96 (10)	104 (20)	105 (20)	135 (12)
Alkalis	0	18 (2)	20 (3)	32 (3)	56 (12)	61 (5)

Numbers in parentheses represent number of patients.

A most detailed study of our treatment statistics fails to show any significant differences to account for recoveries or deaths of coma patients. The primary diabetic state and ketosis were adequately treated with all possible speed in every coma case. Other factors than present accepted lines of treatment must therefore determine coma mortality.

In dealing with the part complications play in coma outcome, it must be kept in mind that we are here considering only the coma itself, and not the general diabetic state of the individual. Thus, one patient was admitted in coma, with gangrene of his right foot. After complete recovery from his ketosis, his foot was amputated and he died in subsequent septicemia. This was a case of death from a complication of diabetes but in no sense a death to be considered in relation to coma statistics. In the total series of 92 cases there were 17 with complications. These included conditions affecting the coma and were mostly due to infections of various types. Of these 17 patients, 10 died. Total coma cases were about equally

divided above and below 40 years of age; but of the 10 total cases with complications, 7 deaths were among those above 40 years and only 3 below the age of 40. Included in these 10 deaths were 2 patients of the conscious group whose deaths occurred later after the ketosis had been controlled and operation for complications had been performed. These have not been classed as ketosis deaths. The only fatal cases complicated on admission by conditions usually carrying a high death rate in themselves were 3 pneumonias, 1 lobular and 2 lobar. Six of the patients who died with complications were autopsied, with findings confirming the antemortem clinical diagnoses.

Discussion. From the analysis of our 92 case histories, it is evident that the mortality in diabetic coma depends primarily on the extent and previous duration of brain damage present when treatment is begun. This central nervous system damage seems unrelated to the severity of coëxisting acidosis, but rather to pursue a course entirely unexplained by present knowledge of coma. Anoxia in the body tissues of highest metabolic activity might well explain the proneness of brain, kidney, liver and heart muscle to be most affected by the serious interference with combustion processes in diabetic coma. Further advance in coma therapy should, it seems, follow this line of investigation.

Diabetic patients with simple ketosis and little mental impairment on admission for treatment seldom die in coma. The remarkably low coma mortality figures cited in many recent articles have been obtained by dealing with early pre-coma cases of low blood alkali reserve, but with slight mental change. This class of patients differs so sharply in response to treatment from the unconscious group that it would seem wise to class them simply as ketosis or pre-coma, and reserve the term *diabetic coma* for only the unconscious cases that have such a high mortality. Present methods of treating the underlying diabetic state are highly effective in pre-coma cases, but are of little avail in a majority of instances of true coma. It would seem that an entirely new line of therapy will be needed to restore function in the tissues damaged in severe diabetic ketosis.

Many previous articles¹⁻⁴ on diabetic coma have been based largely on a classification of patients according to the CO₂-combining power of their blood. We have shown that such selection is not warranted, since this level not only fails to parallel the mental state, but has no proved relation to mortality or prognosis. In our series, the blood CO₂-combining power was higher in those who succumbed than in those who recovered just as it was in the uncomplicated, unconscious cases of Dillon and Dyer. Great advances have been made in the treatment of early acidosis and the prevention of coma since the advent of insulin. Little progress has been made, however,

in the treatment of the unconscious patient with true diabetic coma. General intensive treatment was given all of the cases reported in this series. Insulin as the mainstay of the treatment was used on all. Glucose and alkalis were given in varying amounts, and yet none of these or any other measures employed were able to reduce the mortality of the unconscious patients. It is felt that, even with the closest attention to treatment according to present knowledge, the mortality of the unconscious patient in diabetic coma will be extremely high when the duration of ketosis has been so prolonged as to produce extensive brain damage.

An interesting point which has been shown by our analysis is the frequent occurrence of diabetic coma in the female. There are more females than males with diabetes, but the number of females with coma is far greater than males. It has been noted that coma occurs more frequently during the decades which include puberty and the menopause. The male at this time does not seem greatly affected, since at puberty only one died and at the menopausal decade all recovered. The female, however, at puberty shows a slightly higher mortality (54.5%) than that of the total (51%), but at menopause this mortality rises sharply (81.2%). Such findings are most significant, and lend great weight to the idea that disturbances in other parts of the endocrine system have an important bearing on the occurrence and severity of diabetes.

Age has not been of outstanding significance in our series. In the conscious and semi-conscious group there is some increase in mortality rate above the age of 40. This increase, however, is not great, but enough to indicate that the younger diabetic has a greater chance for recovery. In the unconscious group age plays no significant part, for the mortality is high in all age groups.

Perhaps the most surprising point arising from our case study is that blood CO_2 -combining capacity is of practically no prognostic value in diabetic coma. This finding is directly contrary to prevailing ideas, but seems to be adequately supported by the data presented. No further justification exists for classifying coma cases on the basis of alkali reserve level. Instead there seems every reason that they be grouped only on the basis of brain damage, and that such grouping differentiate the completely unconscious (or true coma cases) of high mortality from the pre-comatose.

Summary. 1. Duration of ketosis, with occurrence of brain damage resulting in unconsciousness, is of primary importance as a prognostic factor in diabetic coma.

2. Lack of prognostic value to be obtained from blood alkali reserve findings is evident from the data we present.

3. The usually accepted methods of treatment are inadequate in the majority of the unconscious diabetic coma patients.

4. Diabetic coma in females seems especially prone to occur at

puberty and in the menopausal decade, and to carry then an exceptionally high mortality.

5. It would seem wise to classify those patients who are unconscious as "diabetic coma," using the term "pre-coma" for all those whose mental state is a much less prominent finding.

The authors are indebted to Dr. C. A. Mills for his constructive suggestions and criticism during the course of the study and in the preparation of the manuscript.

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BOOK REVIEWS AND NOTICES.

PROCEEDINGS OF THE AMERICAN PHILOSOPHICAL SOCIETY FOR PROMOTING USEFUL KNOWLEDGE, held at Philadelphia (Vol. 80, No. 3, February 10, 1939). Contents: Measles and Scarlet Fever in Providence, R. I., 1929-1934 with Respect to Age and Size of Family. By EDWIN B. WILSON, CONSTANCE BENNETT, MARGARET ALLEN, and JANE WORCESTER, Harvard School of Public Health. Pp. 120; illustrated. Philadelphia: The American Philosophical Society, 1939. Price, 75c.

THE behavior of measles and scarlet fever in Providence, Rhode Island, during recent years is compared with previously published data of C. V. Chapin dating from 1858-1923 for measles, and A. S. Pope dealing with scarlet fever covering the period 1865-1924. Percentage distributions, attack rates, and secondary attack rates by age are discussed. An attempt was made to compute rates of incidence which even though rough, since they had to be based on estimated populations, probably give a better picture of the disease than the percentage distributions. Great attention is paid throughout to size of family. Greenwood's theory of the chain binomial was tested and found not to fit when various ways of chaining were considered. The secondary attack rate becomes direct secondary, tertiary, and quaternary if there are three possible secondary cases in a family. The two parts of the measles epidemic of 1931-1932 were compared and differences were found. Measles cases for 1916-1936 for Boston by wards were studied for periodicity and it was found that a 2-year period was not obvious either in total Boston or within the individual wards.

J. G.

TEXT-BOOK OF NEURO-ANATOMY AND THE SENSE ORGANS. By O. LARSELL, PH.D., Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 343; 232 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$6.00.

THE increasing importance of neuro-anatomy in the medical curriculum and the necessity for simple explanations of the functions of the different parts of the nervous system are reflected in the latest addition to the texts on this subject. The general treatment is by functional systems, instead of merely anatomic units, and clinical interpretations are given at the end of nine of the chapters. A number of the figures are from the author's own studies, and there are many new diagrams, some with color. The functions of the hypothalamus and of the cerebellum are considered from the current standpoints. This is essentially a descriptive text, and directions for laboratory work are not included. There are references to current literature at the end of each chapter.

W. A.

FEMININE HYGIENE IN MARRIAGE. By A. F. NIEMOELLER, A.B., M.A., B.S., with a Foreword by WINFIELD SCOTT PUGH, B.S., M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, \$2.00.

THERE are numerous books published upon the rather vague subject of feminine hygiene, of which the author's volume is just one more. It is a small volume, with practically no illustrations. It deals chiefly with menstruation and its disorders, and venereal diseases. The background of

the book is indicated by the publisher's note that all of the illustrations are reproduced through the courtesy of Sexology Magazine. The Reviewer is further prejudiced by the fact that the author does not possess a medical degree.

D. M.

CHEMIE UND PHYSIOLOGIE DES EIWESSES. Mit Unterstützung der Stadt Frankfurt a. M. 3. Frankfurter Konferenz für medizinisch-naturwissenschaftliche Zusammenarbeit am 2. und 3. Juni, 1938. Herausgegeben von Dr. R. OTTO, Geh. Med.-Rat., Direktor des Staatl. Instituts für exper. Therapie und des Forschungsinstitut für Chemotherapie, Honorarprofessor in der med. Fakultät, Frankfurt a. M., Dr. K. FELIX, o. Professor für vegetative Physiologie, Frankfurt a. M., Dr. F. LAIBACH, o. Professor für Botanik, Frankfurt a. M. Pp. 203. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 6.75.

THIS report contains the 17 reviews on the various phases of the chemistry and physiology of proteins given at the 1938 Frankfurt Conference, together with discussions and comments.

First the chemistry of the proteins (protein structure, proteins as constituents of hormones, toxins and enzymes, the influence of proteins on the transport and activity of therapeutic agents) is dealt with. The next section considers the immunologic properties of proteins. The specificity and antigenicity of proteins and their relationship to anaphylaxis and allergy are reviewed; non-specific protein therapy and the allocation of antibodies to the various protein fractions of serum are also considered. The third section discusses certain aspects of the metabolism of proteins, both in plants and in animals, and considers the rôle of proteins in nutrition. Included in this last group are such diverse topics as the detoxification of ammonia and the synthesis of alkaloids by plants, the response of plants to protein decomposition products, the technical cultivation of protein-rich yeasts, plant-breeding experiments on protein-rich "sweet" lupines and on soybeans, protein as a factor in human nutrition, and the utilization of amino acids in the animal body.

This report is markedly inferior to some other recent publications such as the reviews on proteins in the Cold Spring Harbor Symposia on Quantitative Biology. Although the papers in the third section are generally satisfactory, the first two groups, dealing with the structural and immunologic properties of proteins, are distinctly disappointing. Thus, the review on protein structure mentions neither the cyclol hypothesis nor the possible rôle of hydrogen bond formation in the establishment of cross-linkages between polypeptide chains. The discussion of proteins as constituents of enzymes is largely devoted to an exposition of the "carrier" theory of enzyme structure, relatively little being said concerning the nature of the carrier proteins themselves. The papers on immunology present only familiar old material. The most irritating feature of more than half the reviews throughout the book is their failure to give literature references. Even where bibliographies are included, the references may be solely to German work (p. 67) or may contain serious typographical errors (p. 15). More careful editing might have obviated other faults. Thus, on p. 2, the number of amino acids derived from proteins is set at 27; on p. 177, at 22. Further, one cannot detect any apparent relationship between histidine and the indolylpyruvic acid mentioned on p. 182. The statement on p. 171 that milk proteins fed to human beings have a biologic value of less than 50 is surprising. Typographical errors in addition to those on p. 15 were noted on pp. 56, 73 and 172.

Taken as a whole, the reviews are less interesting and valuable scientifically than they are for the information they give about the trends of protein

chemistry and physiology in Germany at the present time. Reviews on the more fundamental aspects of protein chemistry and physiology present nothing essentially new. Indeed, such papers frequently leave one with the impression that considerable recent significant work has not been covered. In decided contrast, the reviews which deal with the problem of increasing the domestic production of protein in the Reich are replete with references to recent work and with notations of results from unpublished studies. It is evident that Germany's attempt to become self-sufficient has influenced the nature of her scientific research.

A. K.

END-RESULTS IN THE TREATMENT OF GASTRIC CANCER. An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment. By EDWARD M. LIVINGSTON, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital, New York; Assistant Clinical Professor of Surgery, New York University College of Medicine, etc.; and GEORGE T. PACK, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York City; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven and Cornell University Medical College, New York City. With a Foreword by BOWMAN C. CROWELL, M.D., Associate Director, American College of Surgeons. Pp. 179; illustrated. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.00.

The theme of this important monograph might well be stated as "nothing ventured, nothing won." The authors have clearly stated the case for gastric resection in gastric carcinoma when there is a possibility of removing the tumor-bearing area; and by their figures have emphasized the importance of an exploratory operation to determine the operability of the lesion in many cases.

The form of this monograph makes it valuable propaganda in impressing on the surgeon his own responsibility for making the decision which may add years of comfortable life to patients who are too often denied this chance. It will undoubtedly prove a stimulus also to the more uniform reporting of results.

This book should be studied by every surgeon attempting to do major surgery; and as a result it is to be hoped that surgeons will either equip themselves to take proper care of these patients or see the importance of referring them to clinics where they can be properly cared for.

I. R.

TEXTBOOK OF GENERAL SURGERY. By WARREN H. COLE, M.D., F.A.C.S., Professor of Surgery, University of Illinois College of Medicine, etc.; and ROBERT ELMAN, M.D., Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Pp. 1031; 559 illustrations. Second edition. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.00.

The second edition of this excellent textbook has brought up to date many of the methods of treatment of surgical patients. It has, like the first edition, full bibliographies and has the virtue of leading the inquiring student to read the original articles from which information has been drawn. Unfortunately there has been no important change made in the section on appendicitis and a right rectus incision is still advised, but since this is a text for students, the young surgeon may, by the time he is ready to operate, have received sufficient training to lead him to use the safer McBurney incision. Of the many textbooks written for the students of surgery, this one can be placed very high on the list.

I. R.

CLINICAL PATHOLOGICAL GYNECOLOGY. By J. THORNWELL WITHERSPOON, B.S. (Princeton), B.A. and M.A. (Oxon.), M.D. (Johns Hopkins), Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Pp. 400; 271 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

THIS book, based upon the author's teaching course, deals with the common pathologic conditions of the various parts of the female generative tract, discusses the anterior pituitary gonadotropic and ovarian hormones, and the gynecologic disorders of early pregnancy. Each subject is presented so that both the pathologic and clinical pictures of the same disease are discussed at the same time.

The author offers it as an introduction to pathologic gynecology rather than as a textbook. The material is well arranged; the illustrations are adequate in number and are well selected, line drawings are supplied in appropriate places. The index is unusually complete for a volume of its size. The book is well rounded in its treatment of the various subjects, though by no means profound. It would seem to be a book ideally suited for the undergraduate medical student, and equally valuable for those graduates who plan to take the examination given by the American Board of Obstetrics and Gynecology.

D. M.

PROBLEMS IN PRISON PSYCHIATRY. By J. G. WILSON, M.D., Senior Surgeon (Retired), United States Public Health Service; Director, Division of Hospitals and Mental Hygiene, Department of Welfare of the State of Kentucky, and M. J. PESCOR, M.D., Clinical Director, United States Public Health Service Hospital, Fort Worth, Texas. Pp. 275; 7 tables. Caldwell, Idaho: The Caxton Printers, Ltd., 1939. Price, \$3.00.

WITH insight born of large experience, the authors have written concisely and lucidly the first book wherein prisoners are classified on a psychologic basis. Its contents are considered under the following chapter headings: Historical Consideration; A Difficult Problem; Attempt to Solve the Problem; The Normal Prisoner; The Feeble-Minded Prisoner; The Psychoneurotic Prisoner; The Psychotic (Insane) Prisoner; The Neuropathic Prisoner; The Homosexual Prisoner; The Recidivist; Discipline in Prison; The Value of Imprisonment; Appendix: Landmarks and Dates in the Development of Prisons.

The real mental defective is accepted as incapable of reformation, unsuited for prison discipline, and should be transferred to a special institution, wherefrom he should not be made a parolee, unless under continuous, competent supervision. In the psychoneurotic group, there is often the background of disrupted homelife and poor health; frequently, such persons feign illness to gain sympathy and for failure to meet environmental difficulties, but such trickery is done unconsciously and so is not true malingering. Among the psychopaths, may be found borderline psychotics, perverts, hoboos, alcohol and drug addicts, cranks and malingerers. The psychotic prisoner comes in for discussion both as to legal insanity and medical insanity; imprisonment as a cause of insanity; insanity as a cause of crime; prison psychoses; malingered insanity; suicide in prison; treatment. Homosexuality is the darkest spot in prison life, with its indulgers, according to different observers, numbering from 10 to 30% of the inmates; extreme measures must be employed to lessen the vice; Russia and Mexico are attacking the problem by "colonization in which the families of the convicts are included or by regular private visits of the husband and wife at stated intervals." "There is no clearly defined, uniform prison policy in the United States . . . Progress in administration along modern lines is impeded by backward and archaic legislature." The value is stressed of spending the last year of a long sentence in a prison camp; of shorter sen-

tences and more efficient parole officers; of more probation, with its numerous advantages safeguarded by additional trained probation officers.

On the wrapper it is stated this volume will appeal to judges, probation and parole officers, social welfare workers, psychiatrists, wardens and staff officers, professors and students of sociology and abnormal psychology. With this the Reviewer is in full accord and begs to add, its compulsory perusal by all trustees on prison boards.

N. Y.

PHYSIOLOGY OF THE UTERUS. With Clinical Correlations. By SAMUEL R. M. REYNOLDS, M.A., Ph.D., Fellow, John Simon Guggenheim Memorial Foundation, The University of Rochester School of Medicine and Dentistry, Rochester, etc. With Forewords by GEORGE W. CORNER, M.D., Professor of Anatomy, University of Rochester School of Medicine and Dentistry, and ROBERT T. FRANK, M.D., F.A.C.S., Consulting Gynecologist, Mt. Sinai Hospital, New York, etc. Pp. 447; 44 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$7.50.

THIS book presents a connected account of many facts of uterine physiology which have not hitherto been assembled. As such it will be welcomed by students of reproductive physiology and interested clinicians. It ought also to be read by those who are unaware of the vitality of this branch of general physiology; that the last decade can account for most of the 1200 references to investigative work considered by Doctor Reynolds is surely proof of the attraction—and importance—of the questions for which so many workers have been seeking answers. The author's own researches, moreover, and his scholarly and very readable review of current concepts of uterine physiology demonstrate anew what an alert mind can do for a subject which, at first glance, is apt to be regarded generally as one of very limited interest.

The phenomena of uterine motility and growth are arranged in relation to the menstrual and the reproductive cycles. Under each of these divisions data which have been drawn from physiologic, pharmacologic, biochemical and endocrine techniques of study are systematically considered. Such a presentation might readily be merely a tedious compendium of facts. Instead, by a critical but fair and attractive selection of data and ideas, the author has woven a patterned account of his subject which should be provocative of much new interest in this field. In particular, it should stimulate obstetricians and gynecologists to restudy certain clinical problems, the physiologic bases of which are clearly and logically defined here for the first time.

The format of the book is attractive, and the typography remarkably free of blemishes.

C. B.

MENTAL DISORDERS IN URBAN AREAS. An Ecological Study of Schizophrenia and Other Psychoses. By ROBERT E. L. FARIS and H. WARREN DUNHAM. Pp. 270; 2 charts, 96 tables and 37 maps. Chicago: The University of Chicago Press, 1939. Price, \$2.50.

THIS is a further contribution in the excellent University of Chicago sociologic series. The foreword by H. Douglas Singer expresses the purpose of this study and publication—"that the environmental setting is an important factor in the etiology of these illnesses (psychoses) has long been recognized; the facts here recorded emphasize the importance and establish for it a statistical validity." Fundamentally the whole study is a good conservative pioneer study in the social aspects of mental disorder. The Chicago area is studied in detail and contrasted with a similar study of Providence, R. I. The authors emphasize the disorganization of the industrial city as contributing to interference with normal family, community

and social life resulting in a causative situation predisposing to and possibly causing schizophrenia and other mental disorders. They do not find this true in reference to organic psychoses.

Psychiatrists will find points with which they will disagree as to the explanations the authors present as reasons why certain psychotic syndromes occur more frequently in certain city areas. But all serious students—psychiatric or otherwise—will find this book an excellent volume to inform them as to the actual picture presented by city life and its influences on psychiatric cases and sociologic conditions. Everyone who is interested in etiology, frequency, distribution, mental hygiene, public health, and any social aspects of psychiatry in a large community should be familiar with this work. L. S.

PERSONAL AND COMMUNITY HEALTH. By C. E. TURNER, A.M., Sc.D., Dr.P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Pp. 652; 127 illustrations, 17 tables, and 4 colored plates. Fifth Edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

THIS book is designed to serve as a textbook of health instruction at the university level. The broad and ever-widening field of knowledge pertaining to health makes the selection of material a difficult task, which the author has well performed. Some of the more important work of the past few years is included in this new edition, which is thoroughly accurate and clearly written, and the book should serve its purpose very well. The first part of the book is devoted to personal health and hygiene and the second part to community health; together they cover the various aspects of health which should be included in a well-rounded university education. The success of the book is indicated by the fact that a new edition has been published every four or five years since 1926. G. R.

NEW BOOKS.

A Textbook of Obstetrics. With Special Reference to Nursing Care. By CHARLES B. REED, M.D., F.A.C.S., Associate Professor of Obstetrics, Northwestern University Medical School; Head of Obstetrical Department, Wesley Memorial Hospital, Chicago, and BESS I. COOLEY, R.N., Supervisor and Instructor, Department of Obstetrics, Wesley Memorial Hospital, Chicago. Pp. 476; 209 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

Practice of Allergy. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 1082; 338 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$11.50.

Studies from the Center for Research in Child Health and Development, School of Public Health, Harvard University. I. The Center, the Group under Observation, Sources of Information, and Studies in Progress. By HAROLD C. STUART, M.D., and Staff. (Monographs of the Society for Research in Child Development, Vol. IV, No. 1, Serial No. 20). Pp. 261; 66 illustrations. Washington, D. C.: Society for Research in Child Development, National Research Council, 1939. Price, \$1.75.

Rétine Humaine et Phénomènes Entoptiques. By DR. E. P. FORTIN. Pp. 207; 127 illustrations (3 in color). Buenos Aires: "El Ateneo," n.d.

The Endocrine Glands. By MAX A. GOLDZIEHER, M.D., Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Pp. 916; 271 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$10.00.

Investigations sur le Glaucome (Essais). By DR. E. P. FORTIN. Pp. 47; 33 illustrations (7 in color). Buenos Aires: "El Ateneo," n.d.

Varicose Veins. By ALTON OCHSNER, B.A., M.D., D.Sc. (Hon.), F.A.C.S., William Henderson Professor of Surgery and Director of the Department of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans, and HOWARD MAHORNER, B.A., M.D., M.S. (Surgery), F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans. Pp. 147; 50 illustrations and 2 color plates. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

Molding and Casting. Its Technic and Application. For Moulage Workers, Sculptors, Artists, Physicians, Dentists, Criminologists, Craftsmen, Pattern Makers and Architectural Modelers. By CARL DAME CLARKE, Associate Professor of Art as Applied to Medicine, University of Maryland School of Medicine. Pp. 308; 69 illustrations. Baltimore: The John D. Lucas Company, 1938. Price, \$4.50.

Provoked Alimentary Hyperglycemia. The Mechanism of the Tolerance Test. By JOSEPH MARSHALL FLINT, Medical Clinic of the University of Lausanne. Pp. 37; 10 illustrations. *The Effect of the Macallum-Laughton Duodenal Extract upon Hypophyseal Diabetes.* By JOSEPH MARSHALL FLINT, and LOUIS MICHAUD, Medical Clinic of the University of Lausanne. Pp. 77; 14 illustrations. Lithoprinted by A. B. Macallum, London, Ontario, 1939.

League of Nations. Bulletin of the Health Organisation, Vol. 7, No. 6 (December, 1938). Pp. 163; 13 illustrations. New York: Columbia University Press, 1938. Price, 65c.

Pseudocystis. By GEORGE DAVIS BIVIN, Ph.D., and M. PAULINE KLINGER, M.A. (A Monograph of the George Davis Bivin Foundation.) Pp. 265; 5 plates and 18 tables. Bloomington, Indiana: The Principia Press, Inc., 1937.

"This monograph is the first attempt to bring together the widespread literature on a very interesting condition. The Principia Press is a company of scholars incorporated for the purpose of publishing meritorious works of learning. All profits are used for the endowment of books."

Medical Microbiology. By KENNETH L. BURDON, Ph.B., Sc.M., Ph.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University School of Medicine, New Orleans; Senior Visiting Pathologist, Charity Hospital of Louisiana at New Orleans, etc. Pp. 763; 120 illustrations. New York: The Macmillan Company, 1939. Price, \$4.50.

The Massachusetts General Hospital. Its Development, 1900-1935. By FREDERIC A. WASHBURN, M.D., Director Emeritus. Pp. 643; illustrated. Boston: Houghton Mifflin Company, 1939. Price, \$4.00.

Textbook of Pathology. A Correlation of Clinical Observations and Pathological Findings. By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine; Chief Visiting Pathologist, Charity Hospital, New Orleans, etc., and HERBERT J. SCHATTENBERG, M.D., Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine; Visiting Pathologist, Charity Hospital, New Orleans. Pp. 681; 383 illustrations and 13 colored plates. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.50.

The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds. By PERRIN H. LONG, M.D., Associate Professor of Medicine, The School of Medicine, The Johns Hopkins University; Associate Physician, The Johns Hopkins Hospital, etc., and ELEANOR A. BLISS, Sc. D., Fellow in Medicine, The School of Medicine, The Johns Hopkins University. Pp. 319; New York: The Macmillan Company, 1939. Price, \$3.50.

NEW EDITIONS.

Medical Mussolini. By MORRIS A. BEALLE, Editor of Plain Talk Magazine. H. C. (CARLYLE) LOWRY, Technical Editor. Pp. 255; illustrated. Fifth Edition. Washington, D. C.: Columbia Publishing Company, 1939. Price, \$3.00.

The aims of this book, but only a mild sample of its character, are to be found in the following quotation from the Preface: "The primary purpose of this book is to head off socialized medicine and its evils. Its secondary purpose is to point out the necessity of ridding the healing arts of the cancerous influence of the Medical Mussolini, and to grant every person the RIGHT to a doctor of his own choice and to the close personal relationship which should exist between the two. And thirdly, it would promote a private system of sickness insurance, instead of the bungling governmental operation of this sociological necessity." It contains a strange mixture of inaccuracies, ignorance, and leanings toward irregular practices, mixed with some ugly truths that require consideration by the discriminating physician. One cannot but regret that such an important subject is so inadequately handled or even suspect whether or not there is some concerted axe to grind. For revisions and additions to this edition, the author expresses indebtedness to the technical editor, H. C. ("Carlyle") Lowry.

Medical State Board Examinations. Topical Summaries and Answers. An Organized Review of Actual Questions given in Medical Licensing Examinations Throughout the United States. By HAROLD RYPINS, A.B., M.D., F.A.C.P., Secretary, New York State Board of Medical Examiners; Assistant Professor of Medicine, Albany Medical College, etc. Pp. 447. Fourth Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, \$4.50.

"This book is an expression of the writer's conviction that the average American medical graduate of today is well prepared for the practice of his profession and consequently that there is little basis for the obvious dread with which he approaches the ordeal of the licensing examination. It is based on fifteen years' experience as Secretary of the New York State Board of Medical Examiners. . . . After a critical survey of many thousands of questions actually used throughout the whole United States a selection of typical questions has been made and these immediately follow the review presented in each of the nine major medical subjects." (From the Author's Preface.)

Diseases of the Mouth and Their Treatment. A Text-book for Practitioners. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., DR. MED. DENT., Professor Emeritus of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, Philadelphia, and SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Professor of Clinical Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania; Visiting Dermatologist, Mt. Sinai Hospital, Philadelphia General Hospital, Home of St. Michaels, and Eaglesville Sanatorium, etc. Pp. 670; 324 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$9.00.

Treatment by Diet. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago, etc. Pp. 691; 1 illustration. Fourth Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, \$5.00.

That a fourth edition has appeared since the first in 1934 proves that the book has achieved its purpose as a "simple, crystallized, practical and workable method of prescribing diets" in health and disease. New material includes chapters on Addison's disease and chronic hyperinsulinism, also extensive revision of the section on vitamins, and others."

Diseases of the Nose and Throat. By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc., and HERMAN J. BURMAN, M.D., F.A.C.S., Adjunct Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc. Pp. 726; 480 illustrations (some in color). Second Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, \$7.00.

PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.,

AND
C. G. JOHNSTON, M.S., M.D.,
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DETROIT, MICHIGAN.

REGIONAL ILEITIS. A SUMMARY OF THE LITERATURE.

History. The description by Crohn, Ginzburg and Oppenheimer⁵² in 1932 of the disease entity "terminal ileitis" focused a great deal of interest upon inflammatory lesions of the small bowel. Numerous surgeons began to report similar experiences. In retrospect, they recalled the confusing picture of a red, edematous terminal ileum complicating some of the appendices they had encountered at operation. They remembered that in an occasional case of so-called appendicitis, the symptoms had not been improved by the performance of an appendectomy, and that perhaps fistula formation and intestinal obstruction had appeared later on. Too, they recalled the case of intestinal tumor that, now and then, presented great difficulties of classification. Taking these data into consideration, and with their attention directed to this type of lesion, surgeons found that terminal ileitis was by no means a rarity, but a disease which they were recognizing more and more in their routine practice.

An investigation of the literature discloses much of interest on the subject of inflammatory intestinal growths. As early as 1806 Combe and Saunders⁴⁷ described what may well have been a case of regional ileitis under the title of "A Singular Case of Stricture and Thickening of the Ileum." Due to the fact that they included no microscopic study of the diseased portion of bowel, this cannot be substantiated with any measure of accuracy; but the gross pathologic description is suggestive.

In John Abercrombie's book, published in 1828,² the author presents a case in a girl of 13 years. The clinical history and gross pathologic

findings are quite compatible with a presumptive diagnosis of regional ileitis.

In 1882 Moore¹⁸¹ for the first time gave a microscopic as well as a gross macroscopic description of a case of regional ileitis with intestinal obstruction in which a colostomy had been performed. The patient died because the colostomy opening was below the site of the obstruction. The author reports the absence of any tubercle bacilli or evidence of carcinoma, and states that the obstruction was due to "long-continued inflammatory changes."

No further mention of this condition is made in the literature until 1905, when Wilmanns²⁸⁴ reported a case of intestinal obstruction following a chronic inflammatory thickening of the ileocecal valve, in which resection of the diseased segment of gut led to complete recovery.

In 1907, Moynihan¹⁸⁶ described simple inflammatory tumors of the large intestine, particularly of the sigmoid flexure, which simulated malignant disease. He furthermore called attention to the frequency of the condition, and attributed some of the cases of so-called cure after colectomy for carcinoma to this mimicry.

In 1908, Robson²²⁴ stated that he had seen 5 cases, in an interval of 12 years, of inflammatory tumors of the large bowel which simulated malignancy.

Perhaps the most important contribution to the literature before the publication of Crohn's original article, was the paper by Braun,²⁹ in 1909, on inflammatory tumors of the intestinal tract. Prior to Braun's article this subject had gone unrecognized in German medical literature, with the exception of Wilmann's isolated case report. Braun reviewed the literature, discovering Moynihan's and Robson's communications. He further attached proper significance to these growths, and reiterated that they were often mistaken for carcinoma due to the fact that microscopic examinations had not been made. He also stated that these tumors had not occurred in the small bowel as far as he knew, and that they had no relation to the specific inflammatory tumors of syphilis, actinomycosis, or tuberculosis. Practically all of the literature dates from the appearance of this article.

Schmidt,²³⁷ in 1911, recorded a case of a tumor involving the large bowel which was wrongly diagnosed preoperatively as carcinoma, but which proved to be an inflammatory growth upon study after resection. In the same year, von Bergmann,²⁷³ in his paper on tumor formation in appendicitis, reported some 12 odd cases, several of which were probably regional ileitis.

A year later, Goto¹⁰¹ listed 2 instances of simple chronic inflammatory strictures involving the terminal ileum and cecum which were misdiagnosed as malignancies. The same author reported 2 similar cases, 1 occurring in the transverse colon and extending as far as the beginning of the descending colon, and the other in the sigmoid flexure.

In 1913, Dalziel¹⁵⁷ published an excellent article in which he cited 4 cases of what he termed "chronic interstitial enteritis." Two of the cases involved the small intestine, 1 occurring in the mid ileum, the lesions in the other affecting over 2 feet of the jejunum. The disease process in the remaining 2 patients was confined to the large bowel, 1 being limited to the sigmoid flexure, and the other to the transverse

colon. Dalziel presented very accurate gross and microscopic descriptions of the resected portions of gut, and further recognized that some of these cases had been mistaken for hypertrophic intestinal tuberculosis. The author stresses the inadequacy of medical treatment and urges surgical intervention with resection of the diseased segment of gut as the recommended procedure.

Läwen,^{162b} in his paper on fibroplastic appendicitis in 1914, advanced the theory that these inflammatory growths were due to extraordinary forms of chronic appendicitis. He ventured to say that the process began in the appendix and then spread to the cecum, ileum, and ascending colon. At the same time, he confirmed the impression of earlier authors that these processes had possibly been confused with hyperplastic intestinal tuberculosis, and proceeded to classify these growths as follows:

1. The inflammatory tumors of the cecum and adjacent ascending colon not having their origin in the appendix.

2. Inflammatory tumors which, to be sure, originate in the appendix, but only implicate this organ to a slight degree and extent either (a) into the anterior or posterior abdominal wall (inflammatory tumors of the abdominal wall after appendicitis, perityphlitic induration of the retroperitoneal tissues, etc.) or (b) into the surrounding intestine and omentum with the formation of connective tissue-like induration and conglomerated tumors (fibroplastic appendicitis in the broader sense).

3. Inflammatory tumors which originate in the appendix and which remain, in the main, localized to the appendix itself, the cecum, ascending colon and terminal ileum (fibroplastic appendicitis in the narrower sense, of idiopathic ileocecal tumor of appendicular origin).

In 1918, Jones and Eisenberg¹³⁴ reported another case of inflammatory tumor of the intestine simulating malignancy. In 1920, Tietze²⁶⁴ published a comprehensive discussion of inflammatory tumors of the large intestine and included in his paper a very complete bibliography. Bachlechner,¹⁰ in 1921, reported several cases of inflammatory ileocecal tumors in which he successfully resected the diseased portions of bowel. In 1922, Fröhlich⁸⁷ noted an interesting case of inflammatory growth involving the cecum in which the preoperative diagnosis had been a tumor of the adnexa. The following year, Moschcowitz and Wilensky¹⁸³ published the first comprehensive survey of non-specific intestinal granulomata in this country. They emphasized the non-specific origin of the disease and also the presence of foreign body giant cells, and commented on the remarkable resemblance of some of the cases to hyperplastic tuberculosis of the intestines. They furthermore reviewed the literature on the latter subject, and arrived at the conclusion that this form of tuberculosis was rather uncommon, and that many of the cases of so-called "hyperplastic tuberculosis of the colon" were in reality simple inflammatory processes. In the same year, Tenckhoff²⁶² and in the following year, Barth¹⁷ reported on fibroplastic appendicitis and concurred with Läwen in the opinion expressed by the latter that these tumors were of appendicular origin.

In the ensuing years, many isolated reports of similar observations appeared in the literature. Horsley,¹¹⁹ in 1925, described a case of typical regional ileitis. Metge,¹⁷⁵ in the same year, described a similar

process in the mid enteron, and analogous conditions were cited in Cabot³⁴ (Case 12133), in 1926. In this year also, there was reported a case by Markiewitz¹⁷¹ involving the cecum. In 1927, Razzaboni²²⁰ speculated as to the possibility of a virus as the etiologic agent of these growths. In 1928, Most¹⁸⁴ reported on inflammatory tumors of the stomach and ileocecal region, and in 1931 A. Fischer⁸⁰ also published a case of regional ileitis. The same year, Mock,¹⁷⁹ in a rather complete review of the literature, discussed infective *granulomata* in great detail and concluded that they comprised a definite pathologic entity. A year later, Golob⁹⁹ published an article on the same condition.

However, the importance of this disease process was not fully realized until 1932, when Crohn, Ginzburg and Oppenheimer published their observations. Since that time numerous articles of importance on the subject have found their way into the literature, and the original concepts of the disease have been considerably modified.

Etiology. Numerous authors have put forth different theories as to the causative factor involved in the production of this disease. So varied are the etiologic agents suggested, that coherence may be obtained only by grouping them in classes, the members of each category being characterized by some common factor.

1. **BACTERIA.** Several bacteria have been implicated as the etiologic agent, but as yet there has been no conclusive evidence to establish any one organism as the sole cause of regional ileitis.

(a) *B. Coli.* Erb and Farmer⁷² gathered some evidence which would seem to point to a member of the *B. coli* group as the etiologic factor. In a stained section of the involved portion of gut they found Gram-negative bacilli. They also isolated an organism from the ileal ulcers, the mesentery, regional lymph glands, liver and gall bladder, which proved to be *B. coli* or a close relative upon laboratory examination (culture obtained 8 hours postmortem; body kept in refrigerator in the interim). However, Erb and Farmer failed to perform agglutination tests with the patient's blood.

Ross²³⁰ also found evidence of a similar character in a case which he encountered.

Numerous other investigators have failed to corroborate these findings and, although they may be interesting, they nevertheless represent isolated instances without proper controls and as such, are quite inconclusive.

(b) *B. Dysenteriae.* Felsen has made repeated claims for this organism as the causative agent. This investigator has completed thorough clinical and laboratory studies and has come to the conclusion that there is a causal relationship between bacillary dysentery and regional ileitis. Bacillary dysentery, Felsen asserts, is not a stereotyped disease constantly involving the same portion of the intestinal tract, but rather a disease with protean manifestations, exhibiting itself in many bizarre forms. When it involves the terminal ileum in an acute inflammatory process it produces a red, thickened, boggy, edematous loop of bowel sharply demarcated from the adjacent normal tissue. There is also present an accompanying acute mesenteric lymphadenitis affecting the regional lymph nodes. In most cases the acute ileitis tends to subside, but some instances have been noted in which the condition progressed

to the chronic non-specific stage with fibrosis and stenosis of the intestinal lumen. Felsen has fairly consistently succeeded in obtaining cultures of *B. dysenteriae* (Flexner or Sonne-Duval) in the acute stages of the disease. He states that, if the diagnosis is to be made, then early culture of the feces and repeated agglutination studies are necessary. It is Felsen's belief that *B. dysenteriae* and the specific agglutination titre usually disappear in those patients in whom the acute lesions fail to heal, due to the complication of secondary non-specific infection. However, he cites an extremely interesting case with a history of regional ileitis of 10 years' duration, in which a resection was performed and bacteriophage and cultures were both positive for *B. dysenteriae*.

In spite of these rather consistent findings, numerous other investigators employing thorough examinations, have failed repeatedly to recover *B. dysenteriae* in one form or another. Hence, although this organism can and does undoubtedly produce a lesion resembling that in regional ileitis, nevertheless the claim of Felsen that it is the sole cause has not been established.

(c) *Tubercle Bacillus*. Due to the remarkable similarity in appearance between the chronic stage of regional ileitis and hyperplastic intestinal tuberculosis, it has been thought by some that the tubercle bacillus is the cause of both conditions. This similarity is further enhanced by the frequent appearance of giant cells in sections of diseased gut in regional ileitis. However, repeated sections stained for the tubercle bacillus have always been negative, as have countless guinea-pig inoculations. The tubercle bacillus may therefore be ruled out as the etiologic agent.

(d) *Mycobacterium Johnei*. Because of the gross resemblance of the lesions of Johne's disease in cattle to those of chronic regional ileitis, Williams²⁸² attempted to demonstrate some relationship between these two entities by injecting johnin subcutaneously into patients with regional ileitis and also into normal controls. However, there proved to be no demonstrable relationship.

(e) *Other Bacteria*. Konjetzny^{149a} found Gram-positive cocci in the submucosa and in the exudate of the bowel of 1 patient. The identity of the organism was never determined and it is not unlikely that it was a secondary invader. Fischer and Lürmann⁸¹ found enterococci in the stools, and Peters²⁰⁵ likewise found enterococci, as well as *Bacillus acidophilus*. Mixer¹⁷⁷ isolated an anaërobic streptococcus from the peritoneal fluid, regional lymph nodes and ulcers in a patient with regional ileitis. Albrecht⁴ isolated an organism similar bacteriologically to *B. pestis* from a case of ileitis with involvement of the cecum and ascending colon, as well. Halligan and Halligan¹⁰⁷ found *Aërobacteria aërogenes* in pure culture in the peritoneal fluid of a case of regional ileitis. The value of this cannot be estimated since there was free perforation into the peritoneal cavity, and the organism may have come from the intestine.

Again, these are observations which are of interest, but which fail to give a clue as to the exact etiology of the disease due to their wide variability and lack of consistency. For the most part, although numerous attempts have been made to recover and identify organisms by anaërobic as well as aërobic cultural methods, by various staining

technique and animal inoculation, the vast majority of these efforts have failed. As Pumphrey²¹⁵ has well stated, in cases where it could be reasonably assumed that the specimens were obtained without fecal contamination, there was commonly no growth of a bacterium.

2. BACTERIAL TOXINS. Erdmann and Burt⁷³ believe that the course of events in regional ileitis is somewhat as follows: A break in the mucosal continuity of the intestine occurs due to the presence of certain toxins. Subsequent to this mucosal ulceration, active infection ensues and makes its way into the wall of the bowel, producing here a low-grade inflammatory reaction characterized by cellular infiltration and connective tissue proliferation. This tenet seems quite unlikely, since similar lesions have not been encountered in other conditions in which mucosal ulceration exists.

3. VIRUSES. Razzaboni²²⁰ described a case of regional ileitis in which numerous eosinophils were present in the sections of the diseased portion of the bowel. The patient also had an anemia, and the author suggests the possibility of a virus infection as the etiologic factor. Stafford²⁵² also suggests the possibility of a virus infection as the cause of regional ileitis because of certain similarities in the clinical course, and to a lesser extent, in the pathologic picture between regional ileitis and lymphogranuloma of the intestine, the latter a known virus disease. At present, however, there is no real evidence in support of this theory.

4. PROTOZOA. The *Entamoeba histolytica* has been considered by some, notably Corr and Boeck,⁴⁹ as a possible cause of the disease. These investigators described a case in which amebiasis as the cause of the lesions was repeatedly suggested during the clinical course of the disease. *Entamoeba histolytica* had been recovered from the stools at various intervals during the 7 years' duration of this disease in their patient. At autopsy, the pathologist called attention to "the undermined edges of the ulcerations" as indicating amebic infection. However, various other findings were listed by the authors as being contradictory to amebic etiology: (a) The colon and lower ileum were practically uninvolved; (b) the stenotic lesion and the hypertrophic polypoid growths are not characteristic of amebic infection; (c) amebic dysentery does not extend into the upper ileum as it did in this case (distal 5 inches of ileum were uninvolved, but the rest of the small intestine with the exception of the proximal 3 inches was marked by ulceration and polypoid masses); (d) there was no pus or blood in the diarrhea.

Other investigators have failed to find the *Entamoeba histolytica* in countless stool examinations of numerous cases of regional ileitis. It is not unlikely, as Corr and Boeck suggest, that this organism was a secondary invader in their case, and that the amebiasis had been cleared up with proper treatment, but the regional ileitis had failed to respond to medical therapy.

5. METAZOA. Many writers, especially in Europe and Asia, have described inflammatory growths of the large intestines produced by *Trichocephalus*, *Oxyuris vermicularis*, *Giardia lamblia* and other parasites.^{12,264} Recently, Barbour and Stokes¹² described an interesting case in a medical missionary with a history of alimentary infection by *Entamoeba histolytica*, *B. typhosus*, *B. paratyphosus* and *Giardia*

lamblia. They ruled out *Entamoeba histolytica* as playing a rôle in the etiology of the present disease because of the involvement of small intestine alone. Likewise, they excluded *B. typhosus* and *B. paratyphosus* due to the widespread pathologic changes in the small bowel (throughout the small intestine there were 13 inflammatory portions, the first being 21 inches from the pylorus and the last $4\frac{1}{2}$ inches from the ileocecal valve). Due to the fact that the *Giardia* infection was present up to the time of death and *Giardia* cysts were repeatedly recovered from the stools, the authors implicated this parasite as the primary cause of the lesions. Obviously, it is difficult to estimate the importance of these findings due to the numerous complications.

Although these parasites can produce a lesion greatly resembling regional ileitis, they cannot be regarded as the usual etiologic agent in view of the fact that repeated stool examinations in nearly all the cases of regional ileitis have failed to disclose the presence of any of the metazoan worms.

6. **ACHYLIA GASTRICA.** Nuboer¹⁹² places etiologic significance upon Achylia gastrica because of the occurrence of this condition in some of the cases of regional ileitis that came under his observation. He claims that, due to the absence of the disinfectant power of the HCl and gastric juice, the microbes multiply and penetrate the intestinal wall. This is probably only a coincidental finding since the vast majority of the cases of regional ileitis have normal HCl and gastric juice present.

7. **ALLERGY.** Kovacs¹⁵¹ mentions the possibility of allergy playing a rôle in the etiology of this disease. Kaijser¹³⁶ described 2 cases of almost identical nature in which there were allergic reactions in the small intestine following intravenous neosalvarsan injections. In both instances the abdomen was opened, and the gross findings resembled those encountered in acute regional ileitis. Kaijser suggests that many cases of so-called localized ileitis are possibly allergic bowel manifestations. Likewise, Cassirer³⁸ cites a patient of Harrington, who on account of severe abdominal pain with simultaneous Quincke's edema was operated on and a "thickened and contracted" segment 6 cm. long was found in the lower ileum. Kraemer¹⁵² calls attention to the prominent enlargement of the regional mesenteric lymph nodes in regional ileitis, and suggests that possibly the disease is primary in the lymph nodes with a secondary allergic spread to the intestine by way of the mesenteric lymphatics due to an overwhelming dose of infective agent.

As yet, there is no substantial evidence to support the allergic hypothesis as the etiologic factor in the production of regional ileitis.

8. **FOREIGN BODIES.** Foreign bodies have been implicated by many as the cause of non-specific inflammatory intestinal granulomata. Jaffe¹²⁵ reported a case in which a fish bone was found. Tietze²⁶⁴ noted an instance of cecal granuloma following appendectomy in which the silk thread used to ligate the appendix was discovered. Schreiber²³⁹ listed a case of ileocecal granuloma containing numerous plum and cherry pits. Morian¹⁶² and Jaffe¹²⁵ recorded the finding of a piece of bone in a granuloma of the colon.

While a foreign body may undoubtedly produce a non-specific inflammatory growth in the intestine, this is obviously not the ordinary etio-

logic agent, since in the great majority of cases of regional ileitis, diligent search has failed to reveal the presence of foreign bodies.

9. TRAUMA. Pupini²¹⁶ reported a case of stenosis of the small bowel due to trauma. The patient suffered a severe blow at the level of the umbilicus, which caused immediate intense pain. Operation 2 months later revealed a 10 cm. segment of the middle ileum with an intensely hyperemic serosa, infiltration of the muscle walls resulting in a rigid thick tube, and also an annular stenosis of the intestine in the involved region.

Reichert and Mathes²²² reported a similar case.

Leonardo¹⁶⁴ published a case in which the terminal ileum, cecum, and ascending colon were the site of a non-specific granuloma. The cause of the disease he attributed to secondary infection due to slight trauma to the ileocecal region in the course of a previous "Robbin operation" for an adherent retrocecal appendix, through a small gridiron incision.

These, too, are the exception rather than the rule and cannot be interpreted as the sequence of events in the ordinary case of regional ileitis.

10. NON-SPECIFIC INFLAMMATION OF THE APPENDIX. As early as 1914, L  wen^{162b} cited cases of intestinal non-specific granulomata involving the ileocecal region which he thought were due to an extraordinary form of chronic appendicitis called fibroplastic appendicitis. He interpreted this process as starting in the appendix and spreading to the cecum, ileum and sometimes the ascending colon. In this same article he reports cases of tumor formation which were described by von Bergmann in 1911. Although it cannot be stated with certainty, probably some of the cases listed by von Bergmann²⁷³ were instances of regional ileitis. Bachlechner, in 1921, also indicated a belief that the appendix might be the offender in some of these cases. Tenckhoff,²⁶² Barth,¹⁷ and Zwerg²⁸⁹ described similar processes. Fischer⁸⁰ claims that possibly the changes in the ileum and mesentery are secondary to chronic mesenteric lymphadenitis which results from an appendicitis, the latter condition being capable of healing. Kapel,¹⁴⁰ however, denies this, stating that in too many cases the mesentery is found to be normal. More recently, Ravdin and Rhoads²¹⁹ have pointed out the similar pathologic pictures in fibroplastic appendicitis and the chronic stages of regional ileitis.

It is interesting to note that many of the patients who come to operation with regional ileitis have had previous appendectomies. The intervals between these operations have varied from a few weeks to many years. However, it seems unlikely that the appendectomy which often preceded the symptoms and signs of regional ileitis by a number of years could be closely related to the latter. Especially is this so in the light of the fact that the inflammatory granuloma often occurs at quite a distance from the appendix. Too, in many patients with regional ileitis, the performance of an appendectomy fails to relieve the symptoms and often leads to fistula formation. Hence, while appendicitis may sometimes play the r  le of an etiologic agent, nevertheless, the finding in numerous cases of regional ileitis of an appendix grossly and microscopically normal precludes the implication of this organ as the usual primary seat of the pathologic process.

11. **IMPAIRMENT OF THE BLOOD SUPPLY.** An impairment to the blood supply of the gut has been followed by granulomatous changes in the area supplied by the affected vessel. Such lesions have been encountered following intestinal obstruction, recurrent partial volvulus, mesenteric thrombosis, hernial incarceration and intussusception. In these cases, vascularization through collateral channels is ample to ward off necrosis of the muscular and fibrous layers of the gut. Ginzburg and Oppenheimer⁹⁴ state that such vascularization is not adequate for the mucosa to regenerate to any extent. As a result, ulcerations of the mucosa occur and secondary infection sets in, followed by connective tissue proliferation producing stenosis of the bowel lumen. These authors find the final picture in such instances analogous to that produced in regional ileitis.

Bockus and Lee²⁶ discuss the possibility of some peculiarity of the anatomy in the terminal ileum, its mesentery and blood supply as contributing to the formation of an inflammatory mass. Quoting Batson, who states that the terminal branch of the ileocolic artery supplying the terminal ileal segment may undergo a good deal of rotation, they conceive of the possibility of this vessel being twisted or pinched by an extraordinary mobility of the terminal ileum, leading to the pathologic changes characteristic of regional ileitis. This, however, would presumably not apply to similar lesions occurring elsewhere in the intestinal tract.

DeCourcy⁶⁰ described a case of regional ileitis in which he felt that he "was dealing with a thrombus of the small terminal vessels of the gut wall with inflammatory extension in both directions along the layers of the bowel." He concluded that if this was true, then possibly ileitis was not a distinct pathologic entity but a complication which might take place anywhere in the intestines.

Bell,²⁰ however, in an experimental study dealing with interference of the blood supply to the gut, was not able to produce a granulomatous lesion, ulceration of the mucosa, or any other lesion resembling those in regional ileitis, and concluded that the pathologic changes in this disease were not due to inadequate blood supply.

12. **INTERFERENCE WITH THE LYMPHATIC SUPPLY.** Bell²⁰ also speculated as to whether the etiologic agent might be mucosal infection spreading to the wall of the intestines and producing edema of the mesentery due to insufficient lymphatic drainage, or whether the infection began as a lymphangitis and then involved the wall of the gut.

More recently, Reichert and Mathes²²² described a series of experiments in which they produced chronic lymphedema of the ileum and colon by injections into the mesenteric and subserosal lymphatic vessels of various sclerosing materials. Employing the intravenous injection of bacteria together with the lymphatic sclerosing preparations, they were able to produce edema and extreme thickening of the wall of the bowel, which changes seemed to be permanent. Reichert and Mathes believe that regional ileitis is characterized by a low-grade chronic lymphatic infection with an accompanying chronic lymphedema. The greater severity of the pathologic changes in regional ileitis as compared with the experimental results, they attribute to the persistence of a chronic low-grade bacterial infection. The observa-

tions of Homans, Drinker, and Field¹¹⁸ that the streptococcus may produce lymphatic obstruction resulting in lymphedema of the lower extremities lend credence to the work of Reichert and Mathes.

13. **HEREDITY.** Crohn^{51c} reported a case of familial incidence of regional ileitis occurring in a brother and sister. He stated that this might be accidental or due to a congenital predisposition or transmissible etiologic factor. However, in light of the lack of evidence and corroboration by others, it is very likely that the former assumption is the correct one.

Since all these various etiologic factors may produce lesions which greatly resemble one another, one must, in the absence of further proof, think of the possibility of regional ileitis resulting from a number of heterogeneous primary irritating agents.

Symptomatology and Clinical Course. The symptoms vary with the location of the lesion and the stage of the disease encountered. Crohn, in his original paper, divided the symptoms into four groups:

1. *Signs of "Acute Surgical Abdomen."* These patients exhibit the symptomatology of an acute intra-abdominal inflammation which cannot be distinguished preoperatively from acute appendicitis. Pain and tenderness are present in the right lower quadrant (if the terminal ileum be involved; pain is higher up if the lesion is in the upper ileum or jejunum) accompanied by generalized colic, fever (up to 103° F.), and a moderate leukocytosis. A mass may be palpable. At operation it is readily seen that the involved segment of intestine is soggy, edematous, reddened, and greatly thickened. The mesentery of this portion of the bowel is also edematous and thickened, and contains numerous large, succulent, hyperplastic lymph nodes. There may be a small amount of clear fluid present in the abdominal cavity. The appendix most commonly shows little sign of pathologic involvement such as mucosal ulceration, but may be slightly reddened due to its proximity if the granulomatous lesion be in the terminal ileum or cecum. Occasionally, the appendix is seriously diseased as revealed by gross and microscopic study. Indeed, an abscess may be found. Attempted drainage may lead to the formation of a chronic intractable fistula after operation.

2. *Symptoms of Ulcerative Enteritis.* These patients have colicky abdominal pain, a low-grade diarrhea with stools containing mucus and blood, but no grossly visible melena. There is also found malaise, marked weight loss and a secondary anemia. This anemia may become very severe as the disease progresses, and the patient may suffer a marked loss of strength. Rarely is tenesmus seen, and the gripping at stool and urgency characteristic of colitis and rectal disease are absent. Moderate fever, intermittent in type, is commonly seen, there being periods during which the patient is apyrexia.

3. *Symptoms of Chronic Incomplete Intestinal Obstruction.* The stage of ulceration is followed by the stenotic phase. However, the latter may appear with or without the patient having experienced the symptoms of one of the previous stages, for occasionally the first indication of the disease may be the signs of incomplete intestinal obstruction. This obstruction is due to the extreme thickening of the wall of the

intestine with resulting narrowing of the intestinal lumen. Severe abdominal cramps, borborygmus and visible peristalsis are the chief complaints. The pain may be temporarily relieved by defecation, only to return a short while later. There may be vomiting which is, however, usually intermittent in type and is not that of impending obstruction. A mass is usually present in the lower right abdomen since the terminal ileum is most commonly the site of the disease. However, with upper ileal or jejunal involvement, the mass may be higher up in the abdomen. Not uncommonly the mass may be palpated in the left lower quadrant in those cases in which there are adhesions and fistulous communications with the sigmoid.

4. *Chronic Fistula Formation.* These fistulas occur very late in the disease and have formed as a result of the slow perforation of the ulcers, or following drainage of an intra-abdominal abscess. In the latter instance, they may occur months after the original drainage operation for a supposed appendiceal abscess. In contradistinction to fistulas of appendicular origin which tend to heal, these fistulas fail to close spontaneously, and resist simple operative closure by excision and inversion of the stump. These fistulas are of various types: (a) Internal—from the ileum, or involved segment of bowel to any of the surrounding hollow viscera, particularly to the sigmoid, cecum, transverse colon, rectum, vagina, uterus. (b) External—from the ileum, or involved segment of bowel to the abdominal wall, invariably following the line of scars of previous operations. These fistulas, when appearing and perishing after an appendectomy for a supposed acute appendicitis has been performed, are almost diagnostic of regional ileitis. (c) Fistulo-in-ano—Crohn^{54a} states that 15% of all cases of regional ileitis are accompanied by perirectal abscesses or perianal fistulas, which may occasionally be one of the earliest manifestations of the disease.

Roentgen Findings. Although the diagnosis may be suspected clinically, nevertheless, it cannot be established with certainty unless a roentgenologic examination be done. Satisfactory Roentgen examination of the small intestine may be accomplished by the following methods. A barium sulphate enema is given under roentgenoscopic control until the terminal ileum is filled by reflux through the ileocecal valve. The large intestine is then emptied by defecation and the ileum remains filled with the contrast fluid. Although satisfactory for the terminal ileum, this procedure is obviously unsatisfactory for lesions higher up in the small intestines. The upper segments of small intestine may be studied by following the progress of a simple mixture of barium sulphate and water through the segments, as recommended by Kantor.¹³⁹ The standard opaque meal is given on an empty stomach and all the films are taken with the patient prone. In this position the ileac loops are more widely separated. Observations are made at intervals of 1 hour from the time immediately prior to cecal filling until the normal time of ileac emptying (3 to 9 hours after ingestion of the opaque meal). Changes may be found anywhere in the small intestine from the jejunum to the ileocecal valve, and also in the large intestines. The changes in the colon may either be spasm secondary to ileal involvement, or else the large bowel may itself be involved in the pathologic

process. In the former case, the spasm is intermittent and the barium meal generally fills out the affected areas in normal contour. Kantor describes the following signs:

1. In the early stages of the disease there is found an absence of variation in the diameter of the intestinal lumen, signifying rigidity. As the disease progresses, there is seen a constant filling defect in the affected loop of bowel. The degree of this filling defect depends upon the extent of the stenosis present.

2. The loops of intestine proximal to the filling defect may be abnormal in contour, being irregular in shape.

3. If actual obstruction is present there is stasis and dilatation of the loops proximal to the filling defect. If the lesion occurs in the ileum the stasis may be 9 hours or more after the opaque meal.

4. The "string sign"—a thin, irregular linear shadow which suggests a cotton string and thereby derives its name. This represents the thinned-out barium filling of a greatly narrowed intestinal lumen. It extends throughout the entire region of the filling defect. Weber has proposed the term "twisted cord appearance" as an alternative for "string sign." While it is highly suggestive, this "string sign" is not pathognomonic, and its absence does not exclude regional ileitis. The string sign may be present in other stenosing processes, and has been observed in sarcomas and in syphilis of the terminal ileum. Kantor has pointed out the roentgenologic criteria for differential diagnosis from a filled appendix, tuberculoma, stenosing sarcoma, intestinal syphilis, the line of the right sacroiliac synchondrosis, and normal ileal spasm without organic lesion.

Pathologic Anatomy. In the early acute stage of the disease, the affected portion of the intestine is a blotchy, soggy, edematous mass, greatly thickened and reddened. Its mesentery is also thickened and edematous and contains numerous large hyperplastic glands. The serosa presents a mottled red appearance and often there is found a small amount of serous fluid in the peritoneal cavity. The mucosa may show ulcerations, particularly along the mesenteric border of the bowel. Microscopically, the mucosal ulcerations may be seen to be covered with a layer of fibrinopurulent exudate. The wall of the intestine is also invaded by the acute inflammatory reaction which tends to decrease in severity as the subserosa is reached. The latter is the site of edema, congestion and interstitial hemorrhage but, in contrast to the submucosa, usually does not have many neutrophils. The entire bowel wall, then, is infiltrated by an acute inflammatory granulation tissue.

In the later stages of regional ileitis the pathologic changes have become more advanced. The diseased gut presents the appearance of a thick, firm, rigid, unyielding tube, not unlike a garden hose. Its mesentery is likewise greatly thickened, sometimes to the extent of $\frac{3}{4}$ inch. There is a marked tendency toward perforation, which is combated by the formation of adhesions to the parietal peritoneum, the omentum or adjacent viscera. As a result, when ulceration through all the intestinal layers takes place, the contents of the bowel are not usually discharged into the peritoneal cavity, but either onto the surface of or into another organ. In Crohn's original series of cases, free perforation into the peritoneal cavity had not been noted. Since that

time, however, Arnheim⁸ and Jackson¹²³ have described cases with free perforation and resulting peritonitis. Also, Halligan and Halligan¹⁰⁷ have recorded another instance of perforation, the perforation having been the first sign of regional ileitis. These, however, are the exception rather than the rule (being the only cases of free perforation in the literature). The more usual occurrence is a chronic process with the cavity tending to be walled off by adhesions. The earliest perforations take the form of linear fistulas that have their origin in mucosal ulcerations on the mesenteric border of the intestine, which penetrate the intestinal wall to the subserosa. As the severity of the ulcerations increase and perforation of the sinuses through the wall of the gut occurs, they may lead to the formation of an abscess in the mesentery. If the disease process affects the terminal ileum, this region is usually more involved at the ileocecal valve and the lesions taper off in degree as one proceeds proximally. Very commonly, the diseased segment is sharply demarcated from the normal intestine. The lumen of the bowel is greatly constricted and distorted, sometimes being almost completely obliterated. Often, the loop of intestine proximal to the stenotic segment is greatly dilated. The mucosa is swollen and shows a series of ulcerations on the mesenteric border. Crohn,⁵² in his original article, was uncertain as to whether these ulcerations were the vestiges of the original ulcerative lesions, or the result of shortening of the diseased mesentery, but now believes the former to be the case. The normal intestinal folds are in part destroyed and in part broken up into polypoid masses, and not uncommonly into papillary excrescences. The serosa is thickened and fibrosed, and frequently presents small tubercle-like structures on its surface. It is these which have caused so much confusion and faulty diagnosis at the operating table, leading the surgeon to call the simple granulomatous lesions "hyperplastic tuberculosis of the intestines."

Histologic sections confirm the gross thickening of the intestinal wall. Closer study reveals this thickening to be due partly to hypertrophy of the muscular layer, and partly to an extensive inflammatory process that involves the submucosa, muscularis and subserosal layers with varying amounts of fibrosis. The submucosa also is usually greatly thickened. The mucosa presents various changes. Sometimes the entire mucosa has become eroded; in other instances only the surface epithelium has been destroyed. There are irregular ulcerations lined by a non-specific granulation tissue containing many neutrophils. The mucosa also shows some areas of atrophy and other zones of polypoid hyperplasia. A chronic, non-specific granulation tissue extends diffusely throughout the muscular layer and into the subserosa. This granulation tissue contains nodules or granulomas composed of fibroblasts and histiocytes, and very commonly, of foreign body giant cells. Some believe that these giant cells have resulted from an inflammatory reaction around inclusion particles of non-absorbable vegetable matter which have come to lie at the base of the ulcers and have been entrapped when healing occurred. These observers believe it not unlikely that the vegetable cells possibly contribute to the hyperplastic fibrosis by virtue of their irritant action. However, Pemberton²⁰² states that the giant cell reaction is analogous to that which can be experimentally

produced by injecting animal oils and is a response to a lipoid substance. These giant cells are indistinguishable from the Langhan's type. Dense aggregates may occasionally be present and strongly suggest tubercles. However, Ziehl-Neelson stains, done with a positive control, fail to bring out an acid-fast bacillus. It is interesting to note the position of the giant cells in the case reported by Barbour and Stokes.¹² Here they were restricted to the intermuscular plans and were in close juxtaposition to Auerbach's plexus. These authors suggest that the involvement of Auerbach's plexus may account for the ballooning of portions of the gut which was present in their patient.

Differential Diagnosis. It is important that regional ileitis be differentiated from a number of conditions which may mimic it both in symptomatology and, not infrequently, in gross appearance at operation.

1. *Neoplasms.* Sarcoma and carcinoma of the intestine may simulate regional ileitis surprisingly. So much is this so, that the diagnosis of inoperable carcinoma has been made at the operating table in numerous instances of regional ileitis, and the true condition remained unrevealed until microscopic study of the diseased bowel had been completed. However, as Wakely²⁷⁵ pointed out, carcinoma of the jejunum and ileum is a very rare condition indeed. Sarcoma of the intestines is also uncommon and rarely causes stricture, but when it does, gross differentiation from regional ileitis may indeed be difficult. Biopsy of a regional lymph node or histologic study of a section of the diseased bowel, in these cases, will aid in the diagnosis.

2. *Hyperplastic Intestinal Tuberculosis.* Ulcerative intestinal tuberculosis occurring secondary to pulmonary involvement is by no means uncommon, and very frequently occurs in patients with active pulmonary lesions. This type of intestinal tuberculosis is characterized by the presence of ulcerated lesions scattered throughout the jejunum and ileum, and to a lesser degree in the colon. These ulcers lie more or less in the transverse axis of the bowel, and the serosal tubercles on the external surface give one a means of identifying the lesions.

On the contrary, hyperplastic intestinal tuberculosis of the ileum alone is almost never seen, as Dowdie points out, there having been only 8 cases reported in the literature up to 1931. This condition may or may not be associated with pulmonary tuberculosis, but is usually thought to be a primary lesion because of the failure to find tuberculous infection anywhere else in the body, and also because of the cure produced by resection of the diseased section of intestine. Undoubtedly many cases of regional ileitis have been falsely labeled as chronic hypertrophic intestinal tuberculosis due to the gross and microscopic similarity of the two conditions. The former may present tubercles not of the exact type seen in tuberculosis; there are also quite frequently found in regional ileitis giant cells of the Langhan's type. Final differentiation may be made by guinea-pig inoculation and by staining of the sections of intestine for tubercle bacilli. In all instances of regional ileitis both of these procedures have consistently yielded negative results.

3. *Ulcerative Colitis.* A very important differentiation is that which must be established between regional ileitis and non-specific ulcerative colitis. In most cases, colitis may be recognized by roentgenologic

studies with the opaque barium enema and also by sigmoidoscopy. However, in those forms of colitis involving only the proximal portions of the colon in which there are no lesions of the sigmoid and rectum, differentiation is quite difficult. These cases may be recognized by the spasm deformity of the portions of the colon involved and by the obliteration of the haustra. Clinical differentiation is usually not possible, the final diagnosis being on a roentgenologic basis. Colitis does not usually produce fistulas except in the anal and rectal regions. Also, in colitis, one rarely encounters a palpable mass.

In cases of regional ileitis with colonic involvement there is clinically a slight diarrhea, high temperature, much prostration and abdominal tenderness. In contradistinction to this, a severe colitis with ileal "wash-back" may represent a terminal stage of an intractable colitis with probably 20 to 30 stools a day.

4. *Actinomycosis*. The intestinal form of this disease usually originates in the cecum and frequently results in the formation of a mass in the right lower quadrant. However, this disease is extremely rare both in this portion of the body, and in the United States. The diagnosis is based on the presence of the characteristic yellow "sulphur" granules in the discharge.

5. *Syphilis*. Syphilis of the intestine, although uncommon, may occur both as a congenital and as a primary condition. In the former, the lesions are found most often in the terminal ileum, where the healing of the syphilitic ulceration produces constriction and stenosis. Primary syphilis of the intestine has a predilection for the lower end of the colon and rectum and thus offers no differential diagnostic problem.

MacCollum¹⁶⁹ states that tertiary lesions of the small intestine are usually localized in the jejunum or upper ileum where they appear as flat elevations involving the mucosa and submucosa. Annular strictures may occur at these sites due to the healing of multiple ulcers. Because of the comparative infrequency of this condition and the aid given by the history of syphilitic infection and positive serologic data, this disease should not offer much difficulty in differential diagnosis.

6. *Hodgkin's Disease*. This disease may be differentiated from regional ileitis by histologic examination of a regional lymph node, which will then disclose the typical pleomorphic cellular character of the lesion.

7. *Appendicitis*. In the acute stages it is usually impossible to differentiate regional ileitis from acute appendicitis preoperatively. The diagnosis in these cases can only be made at the operating table. However, Crohn^{51c} has recently called attention to diarrhea as a differentiating symptom between acute regional ileitis and acute appendicitis, the latter condition rarely being accompanied by diarrhea. The above author believes that diarrhea should always arouse the suspicion of acute regional ileitis.

8. *Other Lesions*. Regional ileitis has also, in rare cases, simulated chronic intussusception,³² and twisted ovarian pedicle and cyst.⁵⁴ It must also be differentiated from mesenteric lymphadenitis,²²⁵ post-operative adhesions,^{50,128,238} appendiceal and periappendiceal abscess,^{111,229,116,7,212,132} tuboövarian tumors, cysts, inflammations and abscesses,^{176b,138,87,123} Meckel's diverticulum tumor, cyst, inflammation

or strangulation through its rudimentary band,¹⁴⁰ and localized idiopathic dilatation of the ileum. Final differentiation is again on a roentgenologic basis.

Statistical Summary and Analysis. Of a total of 393 cases in the literature in which the sex was specified, 222 (56.6%) occurred in male patients and 171 (43.5%) in females. Although males predominate over females to some extent, nevertheless the proportion of incidence of regional ileitis is not in the ratio of 2 to 1 as Crohn stated in his original description.

TABLE 1.—SUMMARY OF AGE GROUPS OF CASES OF REGIONAL ILEITIS.

Age group.	No. of cases.	Per cent.
1-10	18	4.7
11-20	68	17.8
21-30	140	36.6
31-40	76	19.9
41-50	40	10.4
51-60	24	6.2
61-70	13	3.4
71-80	3	0.8

Of a total number of 413 cases in the literature with available data concerning previous abdominal operations, 112 (27.1%) have had previous appendectomies performed.

TABLE 2.—SUMMARY OF SITE OF LESIONS.

Region of intestine involved.	No. of cases.
Terminal ileum	261
Terminal ileum and cecum	80
Terminal ileum, cecum and ascending colon	20
Terminal ileum, cecum, asc. colon and transverse colon	1
Terminal ileum and colon	6
Terminal ileum and lower jejunum	2
Jejunum	16
Terminal jejunum and upper ileum	1
Upper ileum	5
Scattered involvement of ileum	1
Entire ileum	1
Mid ileum	13
Ileum (exact location not specified)	29
Entire small intestine (beginning with jejunum)	2
Terminal duodenum and proximal jejunum	2
Cecum	10
Cecum and ascending colon	7
Cecum, ascending colon and transverse colon	1
Ascending colon	4

The author has attempted to include in the group entitled complete recovery only those cases which have had a minimum follow-up of 1 year, during which period there have been no signs or symptoms of regional ileitis after operation. It is realized that such an arbitrary standard is inadequate because some of the cases reported as complete cures may turn up later as recurrences. However, some such standard is necessary for statistical purposes and a follow-up of 2 to 3 months is of little value. On the other hand, the subject is so recent that there are insufficient 5-year follow-ups.

Treatment. The treatment depends upon the stage of the disease and the condition of the patient. In the acute stage of regional ileitis, there is no unanimity of opinion as to the surgical procedure of choice. A considerable number of observers recommend radical surgery in the acute stage (enterostomy, resection, short-circuiting) because of the frequently progressive character of the disease.^{15,23,25,46a,49,90,94,111,145a,165,177,211} On the other hand, the more recent tendency has, for the most part, been toward a conservative mode of therapy. By conservative treatment is meant an exploratory laparotomy with no operation on the

TABLE 3.—SUMMARY OF OPERATIVE PROCEDURES EMPLOYED AND RESULTS.

Type of procedure.	Total number of cases.	Complete recovery.	Partial recovery.	No improvement.	Recurrence.	Deaths.	Too recent to evaluate recovery or no adequate follow-up.	Remarks.
Resection	290	197 (67.9%)	17 (5.8%)	11 (3.8%)	18 (6.2%)	21* (7.2%)	23	1 died 2 yrs. postop. of cirrhosis seen at op.; no sympt. of ileitis postop.; ²⁸⁷ 1 well for 3 mos. postop.; died 4 mos. postop. of perf.-aut. rev. severe ileocolitis; ²⁸¹ 2 dev. acute int. obst. 1 mo. postop. due to fibrous band constr. ileum; div. of band led to compl. rec. ^{25,134}
Short-circuiting	88	27 (30.6%)	10 (11.3%)	5 (5.7%)	26 (28.4%)	7* (7.9%)	14	3 dev. pern. anem. postop.; 1 devel. beriberi. ²⁰²
Appendectomy	70	39 (55.5%)	2 (2.9%)	8 (11.4%)	6 (8.6%)	3 (4.3%)	12	1 died 2 mos. postop. of meningitis without abd. sympt. —aut. ref. ¹⁰⁴
Exploratory laparotomy	24	2	2	5	1	9	5	9 were of acute type res. in 3 deaths, 2 compl. recov., 1 part. recov.; 3 too recent to evaluate.
Enterostomy	16	6	..	5	1	3	1	
Resection and enterostomy	12	6	2	1	1	2		
Drainage of abscess	5	..	1	3	1	
Closure of perforation	1	1	Acute free perforation. ¹⁰⁷
Separation of adhesions and closure of perforation	1	1	

* 3 deaths in Dixon's series⁶⁸ of 2-stage resections and short-circuiting operations are not listed in either group separately.

intestine *per se*, or exploration and appendectomy. In the latter instance, it is assumed that the possible resolution of the disease occurs spontaneously, and not as the result of the appendectomy which is regarded as being incidental. The conservative approach was recommended by Meyer and Rosi^{176b} and has since been adopted by numerous others, including Crohn.^{15,31,51a,150,163,170} Meyer and Rosi feel that resec-

tion may be unnecessary if the disease is limited to the terminal ileum and the mesentery is not involved, since they believe that spontaneous resolution may occur in these cases. However, if the mesentery is also attacked by the disease process and is thickened and edematous, then spontaneous resolution is less likely to occur.

There is a fair number of cases in the literature in which spontaneous resolution following an exploratory laparotomy or exploration and appendectomy has occurred.^{23,24,31,72,78,95,150,156,113,1766,212,213,225,242,257,287} Furthermore, there is roentgenologic evidence that spontaneous resolution may occur.^{53,1766,278} In addition, there is direct evidence at the operating table that resolution is possible. Pessagno²⁰⁴ has reported an interesting case in which primary resection was followed by recurrence in a previously healthy portion of intestine. At the final of several operations which was done to repair an enterostomy fistula, large segments of intestine previously seen to have been diseased were apparently normal.

On the other hand, a large number of cases which had been treated conservatively progressed to the chronic stage of the disease. This group is probably larger than would be indicated by a casual inspection, since, in many cases, the appendectomies were not performed by the surgeon reporting the case, and the presence of regional ileitis at the time of appendectomy is unknown. Furthermore, because of the slow progress of the disease, many of the individual reports cannot be evaluated properly due to the lack of adequate postoperative observation. Hence, one does not accurately know how many of the acute cases treated conservatively remain well indefinitely, and how many gradually progress into the chronic stages of the disease.

However, because of the definite possibility of spontaneous resolution in the acute stage, conservatism should be the rule. If the symptoms persist, or if recurrence takes place, then a radical operation can be performed later. Furthermore, the risk in the latter instance will probably be less, because resection will no longer be an unexpected emergency procedure undertaken upon a patient who is not properly prepared. Needless to state, repeated careful observation is necessary in the patient in whom a conservative operation has been performed.

In the chronic stages of the disease, surgical treatment is undoubtedly the sole procedure to be recommended. Berg,²¹ who has perhaps had more experience in this field than anyone else, advises a wide resection of the diseased segment of bowel, the extent of the resection being determined by the amount of lymphadenopathy. When the disease is confined to the terminal ileum, he recommends a wide resection of the latter together with the cecum and ascending colon, and an anastomosis between the remaining ileum and the transverse colon. Mixer and Starr,¹⁷⁸ and many others, believe that an important measure in preventing recurrence is wide excision of the diseased mesentery and its lymph nodes. Mixer¹⁷⁷ also emphasizes the fact that drainage should be avoided whenever possible in order to minimize the danger of fistula formation.

Dixon⁶⁶ is of the opinion that an ileocolostomy is to be utilized if the condition of the patient is poor, subsequent resection depending on whether the symptoms disappear or recur. Short-circuiting operations

have completely relieved the symptoms in only 30.6% of the patients in whom this procedure was used, however. In a greater number of instances, the disease progresses despite this procedure and the symptoms return, resection finally being necessary. Numerous authors believe that a short-circuiting operation *per se* is dangerous and insufficient because it leaves behind the area of diseased bowel as a source of infection and extension of the disease process. The observations of Holm,¹¹⁵ and Estes⁷⁴ demonstrating the dilatation of a closed loop of terminal ileum left in the abdomen, make it desirable to resect completely the diseased segment of the bowel. Holm states that the side-tracked ileal loop of a lateral ileostomy or ileocolostomy for obstruction of the terminal ileum is likely to become elongated, dilated and ulcerated, and that an enterocolitis with mucosal degeneration will develop. Therefore, he recommends that wherever possible a resection should be done either primarily or at a second operation.

An interesting observation has been made by Pemberton and Brown²⁰² concerning the results which they obtained in some of their patients, employing the short-circuiting type of operation. In 3 of their cases a deficiency syndrome developed with the blood picture of primary pernicious anemia. It was not possible to determine whether the anemia was related in any way to the ileitis. In another case, they noted the development after operation of a deficiency disturbance comparable to the wet variety of beriberi. This condition disappeared with proper diet and vitamin B therapy.

On the other hand, a resection of the diseased portion of intestine has completely relieved all symptoms in 67.9% of patients in whom this procedure was employed. Because of the better results with resection, and because of the great risk of further spread if the diseased portion of intestine is not removed, a resection is the treatment of choice in the chronic stages of regional ileitis. Some discussion has arisen as to the choice of a one- or two-stage procedure. Berg²¹ and others^{32,42,285} recommend a two-stage resection because the latter is associated with a lower risk, because the two-stage resection may be less difficult technically, and because there may possibly develop some local immunity on the part of the peritoneum and other tissues after the first stage.

The importance of a wide resection cannot be overemphasized, since recurrence of symptoms after too conservative resection, in which portions of the diseased bowel had been left in place, has not uncommonly been reported.^{61,108,123,138,244} Oppenheimer¹⁹⁶ suggests that the ileum should be divided at least 12 inches proximal to the visible or palpable enlargement. In addition, the entire small intestine should be carefully inspected to exclude the possibility of "skip" areas which may lie between segments of normal small intestines.

Terminology. Numerous names have been suggested and applied to this disease with the result that the nomenclature at the present time is confused by a multiplicity of varying terms—regional ileitis, regional enteritis, terminal ileitis, acute ulcerative ileitis, phlegmon of the ileum, non-specific ileocolitis, ulcerative ileocolitis, regional ulcerative enterocolitis, ileocecal pseudotumor, chronic cicatrizing enteritis, ulcerous stenosing inflammation of the lower ileum, non-specific intestinal

granuloma, Crohn's disease. The continued use of such widely different terms must inevitably produce and further the already existing chaos in the terminology of this disease.

The original name "terminal ileitis" first given by Crohn, Ginzburg and Oppenheimer⁵² when the disease was thought to be confined to the terminal ileum alone is now obviously inaccurate and misleading, as are many of the other terms which limit the disease to the ileum or its lower segment. Hence, the names regional enteritis and chronic cicatrizing enteritis were suggested by others.¹¹¹ These terms, however, are for the most part merely descriptive of the region of the bowel in which the disease process may occur and give no adequate information as to the nature of the lesion. Such vague terms as pseudotumor and Crohn's disease are equally undesirable, since the names signify nothing. Probably the most accurate term and the one which should be universally accepted is "non-specific inflammatory granuloma," specifying the region of intestine involved. The adoption and universal usage of the latter nomenclature would avoid the innumerable synonyms and at the same time give the surgeon a thumb-nail description of the pathologic nature of the disease.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

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VITAMIN A AND NIGHT BLINDNESS.

ALTHOUGH a disturbance of the light sense (night blindness) was reported as early as 1500 B.C. and frequent observations were made of its association with malnutrition during the latter part of the 19th and first part of the 20th centuries, the etiologic relationship was not established until 1925 when Holm demonstrated that rats, after eating a vitamin A deficient diet for 3 weeks, became night blind. The work of Holm has been repeatedly verified. Since then it has been demonstrated that the concentration of visual purple in the retinas of frogs, rats and dogs suffering from severe vitamin A deficiency is very low and may not be present at all. Severe cases of night blindness may be cured by adding vitamin A to the diet. Insofar as is known, vitamin A and its precursors are the only dietary constituents that will produce this effect.

Vitamin A and Dark Adaptation. Wald^{45a,b} studied the relationship of dark adaptation of frog retinas to their vitamin A content. He found that retinas, when light adapted, contained more vitamin A than when dark adapted. If the retinas were removed and then completely bleached, the vitamin A content became much higher. He concluded from these experiments that vitamin A was a precursor of visual purple, which is the photosensitive substance in the dark adapted retina. At the present time Wald's conclusions are accepted by investigators who are working on the subject of dark adaptation and vitamin A deficiency.

In the living eye, but not in the isolated retina, visual purple is synthesized from vitamin A. The synthesis and bleaching of visual purple causes a destruction of the vitamin which must be replaced from the blood stream. Wald has developed a scheme which shows the relation of vitamin A to visual purple and dark adaptation.

Vitamin A—Assay and Human Requirements. Vitamin A is an alcohol composed of an ionone ring with an unsaturated side chain. It was synthesized by Kuhn and obtained in crystalline form by Holms and Corbet¹⁹ in 1938. Of the 30 or more carotenoids, only 4 are known to be precursors of vitamin A. They are alpha, beta and gamma carotene and cryptoxanthin. These 4 compounds contain ionone rings. Beta carotene, the most important of the precursors, contains 2 rings and it has been shown that from 1 of its molecules 2 molecules of vitamin A are formed. The biologic activity of the carotenoids and vitamin A depends on the ionone ring and also on the unsaturated side chain.

Vitamin A can be assayed by three methods, namely, chemical, spectroscopic and biologic. In the past there has been considerable discrepancy in values obtained by the physical and biologic methods. This discrepancy may depend on whether the biologic assay is carried out by feeding saponified or non-saponified material. Better absorption of the vitamin or carotene occurs when they are in the form of esters and, therefore, the saponified material produces greater biologic effect.

Guilberg, Miller and Hughes¹³ describe an experiment in which they determined the minimum amount of vitamin A and carotene required to prevent night blindness. Cattle, sheep, swine and rats showed approximately the same requirements per kilogram of body weight. This indicates that the vitamin is concerned with the general metabolic activities of the body as a whole.

The human requirement of vitamin A has not been definitely determined. Estimates that have been made are based on the work of Jeans and Zentmire,^{21a,b} who used a photometer in making a test of the light sense of a group of school children in Iowa. The children with low powers of dark adaptation were given vitamin A concentrates and their powers of dark adaptation improved. Assuming the premise that the smallest amount of vitamin A necessary to prevent a decrease in the rates of dark adaptation is the minimum requirement, various standards have been stated as follows: Jeghers,²² 6000 I. U.; Stiebeling,⁴¹ 4200 to 5600 I. U.; Edmund and Clemmensen,⁷ 700 to 900 units. The league of Nations Committee²⁵ recommends 2000 to 4000 I. U.

The sensitivity of the retina automatically accommodates itself, within very wide limits, to the intensity of the stimulating light by a process of adaptation. It is a well-known fact that, on passing from a lighted to a darkened room, vision is reduced for a short time and soon becomes greatly improved. The process by which the vision is increased is called dark adaptation. Conversely, the improvement of vision occurring after exposure to a dazzling light is called light adaptation.

Night blindness, which is a condition in which vision is good in ordinary light but poor in dim illumination, results from a defect in the

process of dark adaptation. It was shown to be a quantitative defect in the light sense by accurate measurements of the light thresholds made by Piper in 1903. Aubert (quoted by Adams) (1865) was the first to study the course of dark adaptation but his methods were crude.

Methods of Testing Light Sensitivity. The light sense may be tested by the following methods: 1, Determination of the light minimum by means of a photometer; 2, determination of the visual acuity in low illumination; 3, examination of the visual fields in low illumination; and, 4, determination of the power of distinction in low illumination. The first method is the one of choice because the others test the form sense as well as the light sense.

A determination of the light threshold made with a photometer represents a measure of the sensitivity of a certain area of the retina after a definite period of dark adaptation. If a series of light thresholds of a retinal area are plotted, using the duration of dark adaptation as abscissæ, a series of points will be obtained which, when connected, form a curve. The curve represents the change of the light threshold of the retinal area during a period of dark adaptation.

The actual change only of the intensities will be shown if one uses the actual intensities of the light thresholds in plotting the curve. However, by using the logarithms of the intensity of light thresholds as the ordinates, the curve will show the relative rate of change of the intensities. For example, suppose that after a specified period of time the light threshold decreased from 10,000 to 1000 micromillilamberts. Such a change would represent 1 logarithm unit. Again let us suppose that in the next period of time the threshold was reduced from 1000 to 100 micromillilamberts. The change of threshold is again represented by 1 logarithm unit in the second interval of the dark adaptation. Although the threshold decreased 9000 units in the first period and in the second only 900, in each interval of dark adaptation there actually occurred a 10-fold reduction of the light threshold. It is thus seen that logarithms show the relative rates of reduction of the light threshold.

Studies of the physiology of vision by means of the photometer, the facts known about color blindness, the curve of visual acuity, the critical frequency of flicker, the differences of the latent period, after-image phenomena, the two types of luminosity curves, the differences in chemical and electrical responses in the retina, provide a wealth of information to show that there are two mechanisms of vision. One is subserved by the rods and the other by the cones. The theory of vision, known as the duplicity theory, has an anatomic basis which was first provided in 1866 by Max Schultz. Its acceptance dates from its exposition by von Kries (1896). The essential feature of the duplicity theory is that there are two distinct types of activity in the retina: 1, A scotopic mechanism which is mediated by the rods with which visual purple is closely associated. It is concerned with the appreciation of light and movement. The perceptions are achromatic, are activated by a low threshold intensity of stimulus and, therefore typically evident in conditions of dark adaptation. 2, A photopic mechanism mediated by the cones, which concerns itself with form vision and color vision and which, with a relatively high threshold stimulus intensity, is typically evident in the light adapted eye.

As far as is known, visual purple has been found only in the rods of

the retina. But the failure to recognize it in the cones may be due to its great dilution. Visual purple is bleached by exposure to light and regeneration occurs in the dark. Regeneration is independent of the central nervous system, since it occurs even after the section of the optic nerve. Regeneration is retarded by a deficiency of vitamin A, a circumstance which is probably an important factor in the etiology of night blindness.

Anomalies of the Light Sense. Anomalies of the light sense may be divided into 6 categories as follows:

1. *Result of disease of the eye*—peripheral lens opacities and disease of the periphery of the retina, such as pigmentary degeneration, advanced myopia and chorioretinitis, which affect the periphery more than the fovea. A related failure in adaptation may occur in retinal detachment, optic neuritis and glaucoma.

2. *As a congenital and hereditary condition.* Simple congenital night blindness may occur without any associate anomaly. There may be three tendencies in its hereditary transmission: *a*, A dominate form which was first noted by Cunier (1838), who started the compilation of the famous pedigree of Jen Nougaret, the largest pedigree known for the inheritance of any human condition; *b*, a recessive form, frequently associated with myopia; and, *c*, a recessive sex-linked form, usually associated with a high grade of myopia. This form is transmitted through unaffected daughters of affected males to some of their sons.

3. *Congenital and hereditary night blindness* associated with other anomalies of the retina, such as in Oguchi's disease, and in various types of pigmentary degeneration of the retina.

4. *Pathologic changes in the liver* have been associated with the etiology of night blindness and it forms an occasional symptom of jaundice.

5. The factor of *overexposure to light.* Aykroyd^{2a,b,c} reported this phenomenon and associated it with vitamin A deficiency.

6. Cases in which *no pathologic changes* are evident and nutritional disturbances have been absent. The majority of these have been associated with neurasthenic and other functional symptoms.

Recent Investigations by Photometric Methods. Photometers have been known for almost half a century and, as early as 1896 were used to study the light thresholds of malnourished persons who had night blindness. This instrument did not become popular as a method of detecting subclinical states of vitamin A deficiency until 1934, when Jeans and Zentmire reported that, by means of the photometer, they detected a disturbance of dark adaptation in 21 % of a group of 213 children in Iowa. About one-half of the 21 % were kept in a hospital and given cod-liver oil, and, after a period averaging 12 days (4 days to 6 weeks), all showed improvement in their dark adaptation.

Other investigators have shown that the incidence of vitamin A deficiency is likely to be high if a photometer is used in making the tests. On the other hand, some investigators have not been so successful in finding a high incidence of vitamin A deficiency or even finding a correlation between the variation of photometric determinations of dark adaptation and the vitamin A content of the diets.

Recently Hecht and Mandelbaum¹⁶ published a report of photometric

studies on 4 normal adults who were on vitamin A deficient diets. The subjects showed a change in the powers of dark adaptation of both the rods and cones as soon as 14 days after going on the diet. After 35 days, the threshold of the rods had increased about 1 logarithm unit while that of the cones had increased $\frac{1}{2}$ logarithm unit. The light thresholds of these subjects did not return to normal after many days subsequent to the ingestion of vitamin A or its precursors but remained at high levels even after 70 days. These findings indicate that it may take longer to restore the normal functions of the rods and cones than it does to decrease them by altering the vitamin A content of the diet. These findings are not in agreement with other published results.

Wald and his associates^{45,47} recently reported the results of an experiment conducted on 1 human subject in manner similar to the procedures followed by Hecht and Mandelbaum. The experimental subject developed definite changes in dark adaptation after being on the diet for 4 days. After 25 days, the threshold of the periphery of the retina had increased 1.5 logarithm units. After taking 100,000 units of vitamin A, in the form of carotene in oil in gelatin capsules, orally, the light threshold returned to normal in 38 minutes. This speed in the return of the light sense to normal values after taking vitamin A is of the same order of magnitude as that which has previously been reported, but differs greatly from the very slow rate of recovery of the subjects used by Hecht and Mandelbaum.

Experimental Results: Dermatologic Findings. Lesions of the skin occurring in conditions of malnutrition were described by Wiltshire⁴⁸ in 1919, Nicolau³¹ in 1919, and Aschoff and Koch¹ in 1920. But the relation of these lesions to vitamin A deficiency was not recognized until 1931, when Frazier and Hu¹⁰ reported a form of dermatosis occurring in soldiers who had been living on diets deficient in meats, eggs and green vegetables for periods ranging from 6 months to 2 years. These men were in their early twenties and had reported to the ophthalmologic clinic during February, March or April, 1929, because of keratomalacia.

Nicholls (quoted by Youmans and Corlette⁵⁰) described a papular lesion on dry skins which was frequently accompanied by mild neuritis, keratomalacia or diarrhea among poorly fed laborers in East Africa and among convicts in Ceylon. Because of the roughness of the skin, he named the condition phrynoderma (toad skin). He thought that this condition may be due to other food deficiencies associated with lack of vitamin A, because some of his cases also had dysentery and neuritis.

Loewenthal described a similar dermatosis occurring in prisoners in East Africa who were also afflicted with night blindness and xerophthalmia. Treatment with cod-liver oil for 9 weeks, and without modification of the diet, resulted in cure of the night blindness and xerophthalmia in every case and of the dermatosis in 99%. The average age of the prisoners was 35 years. Loewenthal's description of the dermatosis was concerned with five features:

1. *Dryness of the skin* affecting the whole body, both sebum and sweat being deficient. This change is most marked on the extensor surfaces of the arms, on the backs of the hands and front of the legs

and on all surfaces of the thighs and across the buttocks. 2. *Itching*: a very prominent feature. 3. *Papular eruption* usually on the extensor surfaces of the arms and on the front and outer surfaces of the thighs. The papules were about 0.6 cm. in diameter and smooth-topped. The edges were sharply demarcated. 4. *Folliculitis*: in some cases there was an inflammatory swelling of the hair follicles without pus. Usually there was a broken hair projecting from the center. 5. *Acne*: clinically, the papules differ in no way from those of acne vulgaris except that pustulation is extremely rare.

Goodwin,¹² in London, and Sweet and K'Ang,⁴³ in China, described similar follicular keratotic lesions in association with vitamin A deficiency.

The *histopathological features*, described by Rae,³⁶ are very similar to those described by Frazier and Hu,¹⁰ Loewenthal²⁷ and Nicholls. The description by Rae, taken almost *verbatim*, is as follows:

1. *Epidermis*. There is a superficial hyperkeratosis of the epidermis in all cases. In some places the stratum corneum was very much broadened. There was no evidence of parakeratosis. The keratin was either homogeneous in structure or present in loose meshes. No appreciable changes were present in the stratum lucidum and the stratum granulosum. The rete mucosum in some places, especially in the neighborhood of the atrophied hair follicles, showed moderate hypertrophy. The interpapillary processes were widened and more prominent in these areas. The prickle cells appeared normal but, in places, showed vacuolation in their protoplasm. The cells of the stratum germinativum were apparently normal. Evidence of hyperpigmentation was not marked even in the neighborhood of the papules.

2. *Corneum*. Except for changes in the perifollicular regions, the corneum was apparently normal.

3. *Sebaceous Glands*. The sebaceous glands are not seen in connection with the atrophied hair follicles. Serial sections, however, revealed that the glands were still present in some areas in which the follicular lesions were not very marked. In these areas there was a varying degree of hyperkeratinization of the lining epithelium of the hair follicles. The sebaceous glands showed either a decrease in the amount of cytoplasm or in the number of cells. At a later stage of the follicular lesion, a few cells with very little cytoplasm represented the glands. In typical papules they were atrophied and their site was generally occupied by young connective tissue and mononuclear lymphoid cells.

4. *Sweat Glands*. Changes in the sweat glands were not a marked feature. In some instances, however, the coil glands were few in number, their epithelium was flattened or shrunken and irregular and the lumen dilated. The funnel-like depressions in the epidermis containing the sweat pores were filled to a varying extent with the hyperkeratinous material.

5. *Hair Follicles and Hair*. Marked changes were found in the hair follicles in all instances. The number of follicles affected and the degree of changes present, however, varied. The mouths of the hair follicles showed marked hyperkeratinization of the living epithelium and, as a result, the funnels of the follicles were widened and were plugged by dense masses of horny tissue. Closer examination revealed that the

follicular plugs consisted of concentric lamellæ of flattened cornified cells in which there were no nuclei. In 1 case, instead of the filter-like depression, slight or marked elevations were often found at the mouths of the affected follicles. Sections of the coiled and atrophic hairs or broken hairs were seen in the substance of some of the follicular plugs but pustulation in the latter was not noted in any instance. Serial sections showed that the lower part of the affected follicles was atrophic and was often separated from the upper part of the follicles by delicate fibrous tissue. In some places, however, the lower third of the follicles showed moderate hypertrophy of the external root sheath.

Varying degrees of cellular infiltration, mostly fibroblasts and mononuclear lymphoid cells, were often present in the loose perifollicular tissue; neutrophils, eosinophils and evidences of hemorrhage were not noticed in any instance.

The papules, which constitute the important clinical manifestation of the skin lesions in vitamin A deficiency, arise from the pilosebaceous follicles as a result of non-inflammatory hyperkeratosis of the lining epithelium. The perifollicular infiltration is probably secondary to the irritation of the keratotic plug in the orifice of the hair follicle.

The atrophy of the sebaceous glands is secondary to the plugging of their ducts by keratotic epithelium. However, the absence of sebaceous cysts in all instances would suggest that, apart from the mechanical factor, the nutritional deficiency is also primarily responsible for the atrophy of the sebaceous glands.

A number of other conditions have been described. These include ichthyosis follicularis, lichen planopilaris, pityriasis rubra pilaris, keratosis suprafollicularis, lichen spinulosus, characterized by the presence of horny plugs at the orifices of the hair follicles forming small papules.

Rae states that phrynoderma is a separate entity associated with mal-nutritional states. No experimental evidence has been produced to show that it is definitely due to deficiency of vitamin A alone, since similar changes in the sebaceous glands have been noted in combined deficiencies of vitamins A and B, and also in scurvy by several investigators.

Youmans and Corlette⁵⁰ reported that 6 of the 20 cases of dermatosis they studied showed skin lesions similar to those described above. They also observed that the lesions disappeared when the patient was given cod-liver oil. Photometric studies of some of their patients demonstrated an occasional mild hemeralopia. However, they thought that in some instances the skin lesions may be among the first clinical evidences of vitamin A deficiency.

Vitamin A deficiency produces pathologic changes in many other organs. Most of the changes consist of a keratinizing metaplasia in which epithelium, regardless of its location or function (*i. e.*, bronchi, genito-urinary tract, salivary glands, or stomach and intestines) is replaced by stratified keratinizing epithelium. The first change in the epithelium is atrophy. This is then followed by proliferation of the basal cells to form stratified keratinizing epithelium. This metaplasia is identical in appearance in all locations.

In the rat, the salivary glands and respiratory tract are affected first. The genito-urinary tracts are next involved, and last to be affected are the ocular and paraocular tissues. Administration of vitamin A to

these deficient animals will effect a reversal of the metaplasia and, for some reason, repair is more rapid with butter fat than cod-liver oil. Wolbach and Howe⁴⁹ did not believe that infection was more common in rats deficient in vitamin A but did think that, once infection was started, the process of epithelial repair was retarded. When repair of the epithelium started it was diffuse and sudden, due to the fact that all cells were capable of proliferation. If repair of the epithelium starts before metaplasia is complete, that is, after the original epithelium has been undermined by an epithelium of basal cell origin but not yet developing keratinizing epithelium, it will be completed in from 5 to 13 days. When the metaplasia has been completed and new stratified squamous keratinizing epithelium is laid down comparable layer by layer with the epidermis, repair is complete in 10 to 12 days, but the repair is not in the same stage at all places. The repair of epithelium which is normally either stratified or of the transitional type, as in the conjunctiva or bladder, is complete in 7 to 8 days.

Johnson conducted experiments on rats and found that severe vitamin A deficiency produced degeneration involving several layers of the retina which is probably not reparable. Hart and Guilbert reported cases of night blindness in cattle and sheep resulting from severe avitaminosis A which was permanent, although ample amounts of vitamin A were administered for months in an attempt to cure the visual defect.

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ORIGINAL ARTICLES.

STREPTOCOCCUS VIRIDANS ENDOCARDITIS LENTA.

**A CLINICO-PATHOLOGIC ANALYSIS OF THE EXPERIENCE IN THE
WISCONSIN GENERAL HOSPITAL.**

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THE studies of Osler,⁷ Horder,⁴ Libman,⁶ Blumer,¹ Levine⁵ and Gross and Fried,³ among others, have contributed greatly to the knowledge of subacute bacterial endocarditis. Largely through their efforts a pathologic curiosity among cardiac affections has become a clinical commonplace. Usage has apparently fixed Libman's designation, but the current trend toward etiologic terms would recommend *S. viridans* endocarditis lenta in its stead. The literature on the subject is extensive and comprehensive. Reviews such as those of Blumer¹ and Levine⁵ have thoroughly analyzed the developments in the subject from time to time and in the present communication it is purposed to present and digest simply the clinical and pathologic features of 88 instances of the disease that have occurred in the Wisconsin General Hospital.

In Table 1 the age and the sex incidence of the group are shown.

The male sex predominates in the ratio of 5:3. A divergence in the incidence does not appear until the fourth decade, from which period the male predominance becomes striking (almost 3:1). It is fur-

thermore interesting to note that 60 of 88 subjects (68.1%) were between 11 and 40 years old. The range of ages is quite wide and no decade up to the ninth escaped in this series. The available evidence supports the thesis of a prepared field in the valves for the secondary implantation of a bacterial invader from the focus of infection. Rheumatic valvulitis and congenital cardiac lesions have been accepted as the most common precursors of this form of endocarditis. In the light of this position an analysis of Table 2 is particularly illuminating.

TABLE 1.—AGE AND SEX INCIDENCE.

Age.	Males.	Females.	Total.
1-10	1	1	2
11-20	9	9	18
21-30	13	12	25
31-40	13	4	17
41-50	5	4	9
51-60	9	1	10
61-70	2	2	4
71-80	3	..	3
Total	55	33	88

TABLE 2.—ANTECEDENT HISTORY OF DISEASE.

	No.	%.
Rheumatic fever, alone	36	40.9
Rheumatic fever and tonsillitis	6	6.8
Rheumatic fever and chorea	1	1.1
Rheumatic fever and scarlet fever	1	1.1
Tonsillitis, alone	10	11.3
Scarlet fever, alone	14	15.9
Tonsillitis and scarlet fever	1	1.1
Chorea, alone	3	3.4
Total—rheumatic chain	72	81.6
Congenital cardiac lesions	4	4.5
Syphilis	1	1.1
Hypertensive cardiovascular disease	1	1.1
Pneumonia (type?)	1	1.1

As anticipated, the past history of diseases of the rheumatic chain dominates this phase of the picture; but even forewarned, an incidence of 81.6% exceeded the expectancy. Among the diseases of this group rheumatic fever itself held first place (40.9%) and scarlet fever a poor second (15.9%). A clear-cut history of congenital heart disease was afforded by only 4 (4.5%) of these patients. Only the isolated instance of syphilis among the remaining suspected predisposing factors should be stressed.

Precipitating factors to the actual inception of *S. viridans* endocarditis lenta could be fixed in only a minority of instances. In 9 patients (10.2%) an acute upper respiratory infection had seemed to initiate the disease; but the constitutional symptoms of the endocarditis may readily mislead in this direction. In 6 subjects (6.8%)

there was apparently a direct continuity of an acute episode of rheumatic fever with the attack of endocarditis lenta. In none of these instances were the rheumatic manifestations suggestive of the embolic features of the latter condition. Dental extractions were exciting causes 5 times (5.6%). In one of these patients the constitutional symptoms appeared the day after the extraction of a tooth and embolic phenomena were delayed only a few days. Non-specific prostatitis under treatment by massage was twice indicted. Infected abortion likewise apparently initiated the condition in 2 patients. *S. viridans* endocarditis lenta appeared as a terminal complication in 6 instances (polycystic disease of the kidneys, 1; Paget's disease, 1; benign prostatic hypertrophy with acute retention, 1; cancer, 3). In two postmortems early cancers of the lung and colon were disclosed.

Contrary to the prevailing opinion *S. viridans* endocarditis lenta occurred 5 times (5.6%) in patients suffering from recurrent congestive failure (see Case 1).

Case Reports. CASE 1.—M. O., white male, aged 45, had been admitted to the hospital twice in the preceding 4 years in episodes of congestive failure on the background of rheumatic heart disease with cardiac hypertrophy and dilatation, mitral stenosis and regurgitation and auricular fibrillation. On the third admission, the patient presented the characteristic findings of congestive failure with general anasarca. There was added, however, the experience of chills and general malaise. During the hospital stay of 10 days the temperature ranged from 96° to 104.8° F. The cardiac findings had undergone no perceptible change. The cardiac enlargement, absolute arrhythmia, and the mitral systolic murmur persisted. There was a positive centrifugal venous pulse and general anasarca. The systolic blood pressure was 98. Blood culture confirmed the diagnosis of *S. viridans* endocarditis lenta.

The patient died in congestive failure and at necropsy characteristic vegetations were found on the aortic valve. There was also thickening of the mitral valve, early atrophic cirrhosis of the liver with chronic hepatitis, cholecystitis and chronic passive congestion of all viscera.

Unusual instances of remote but indubitable portals of infectious entry may arise as in Case 2, where an empyema served as such. Unfortunately, the etiology of the pneumonia was not fixed before admission.

CASE 2.—I. G., white female, aged 63, suffered from an empyema complicating pneumonia which antedated the admission by 3 weeks. Her chief complaint upon admission was dyspnea; but chills and fever had continued subsequent to the acute episode of pneumonia. Pain in the left side aggravated by coughing and deep breathing had been pronounced during the 2 weeks preceding admission. Increasing dyspnea had been observed for 2 days. Exploratory thoracentesis had detected the presence of pus in the left pleural cavity. A weight loss of 18 pounds had been noted. No history of rheumatic fever was elicited. The physical examination established signs of fluid in the left pleural cavity.

A moderate hypochromic anemia was established, the lowest level being 50% hemoglobin with 3,240,000 erythrocytes. At this time a leuko-

cytosis of 14,650 with 81% neutrophils was registered. Cultures of the empyema fluid revealed streptococci; and blood culture, *S. viridans*. Death resulted from hemorrhage through the thoracotomy wound of drainage of the empyema. At necropsy, characteristic vegetations of endocarditis lenta were found on the mitral leaflets and there was an isolated abscess in the heart muscle. The pericardium contained Aschoff-like cells and there was an acute embolic glomerulonephritis.

The inception of *S. viridans* endocarditis lenta is notoriously inconstant. In this series, the onset was insidious in 55 (62.5%) and precipitous in 24 (27.2%). In the remaining 9 instances (10.2%) no clinical clue to the underlying infectious process was afforded by the clinical history or the physical findings. The common constitutional symptoms are listed in Table 3.

TABLE 3.—CONSTITUTIONAL SYMPTOMS.

	No.	%.
Weakness	54	61.4
Fever	43	48.8
Weight loss	40	45.5
Chills	36	40.9
Sweats	34	38.6
Headache	27	30.6
Fatigue	11	12.5
General aching	5	5.6

While weakness was the commonest and the most conspicuous constitutional symptom, fever, chills, sweats, weight loss and headaches were very prominent manifestations among this group of patients.

The further symptomatology of these patients suffering from *S. viridans* endocarditis lenta has been grouped under the several systems in the following tables.

TABLE 4.—CARDIOVASCULAR SYMPTOMS.

	No.	%.
Dyspnea	42	47.7
Palpitation	30	34.0
Edema	22	25.0
Precordial distress	21	23.8
Syncope	3	3.4

The most illuminating detail among the cardiovascular symptoms was the relatively high incidence of symptoms referable to congestive failure, dyspnea, palpitation and edema, a circumstance that will recur from time to time in the present analysis. The occurrence of precordial distress was independent of coronary or pericardial involvement.

TABLE 5.—RESPIRATORY SYMPTOMS.

	No.	%.
Cough	29	32.9
Epistaxis	15	17.0
Hemoptysis	11	12.5
Pleuritic pain	7	7.9
Sore throat	4	4.5
Hiccough	1	1.1

The high incidence of coughing may be related to congestive failure. The occurrence of hemoptysis depended upon passive congestion or infarction of the lungs. As a rule the pleuritic pain arose from pulmonary infarction or patchy pneumonia. Perhaps the most significant detail in the present connection was the rather frequent appearance of epistaxis (17%). In all probability this symptom may be attributable to the increased capillary permeability of endocarditis lenta.

TABLE 6.—GASTRO-INTESTINAL SYMPTOMS.

	No.	%.
Anorexia	27	30.6
Nausea and vomiting	22	25.0
Nausea	4	4.5
Pain:		
Left upper quadrant	15	17.0
General	14	15.9
Right upper quadrant	4	4.5
Right lower quadrant	2	2.2
Diarrhea	4	4.5
Dysphagia	2	2.2
Sore tongue	2	2.2

Related to congestive failure, or to the toxemia of the infectious process, anorexia, nausea and vomiting took precedence among the gastro-intestinal symptoms of *S. viridans* endocarditis lenta. From a diagnostic standpoint the distribution of abdominal pain was very important. In 17% of the series (15 patients), pain occurred in the left upper quadrant of the abdomen. Capps' points occurred quite commonly in this group of patients.

TABLE 7.—GENITO-URINARY SYMPTOMS.

	No.	%.
Amenorrhea	7	21.2
Hematuria	4	4.5
Pain—left flank	3	3.4

In the past apparently too little attention has been paid to the rather common occurrence of amenorrhea. If 4 of the 33 women of this series be excluded as without the usual age period of the menacme, an incidence of 24.1% among the remaining 29 is quite significant. The relative infrequency of gross hematuria could be anticipated from the order of the pathologic process, *viz.*, focal embolic nephritis.

TABLE 8.—SYMPTOMS REFERABLE TO BONES, JOINTS AND MUSCLES.

	No.	%.
Joint pain	26	29.5
Pain, extremities	13	14.7
Pain, left shoulder	8	9.0
Tremor	4	4.5
Backache	3	3.4

Among the symptoms grouped in Table 8 only the pain in the left shoulder requires especial analysis. Infarction of the spleen with diaphragmatic irritation was naturally suspected as the most plausible explanation.

TABLE 9.—NEUROLOGIC SYMPTOMS.

	No.	%.
General: Nervousness	4	4.5
Insomnia	2	2.2
Unconsciousness	2	2.2
Drowsiness	1	1.1
Central: Meningeal: Stiff neck	1	1.1
Special sense: Vertigo	14	15.9
Tinnitus	3	3.4
Amblyopia	13	14.7
Peripheral(?): Paresthesia	30	34.0

These data are quite scattered and probably the sole illuminating detail is the high incidence of paresthesias (34%).

Passing to the physical findings, the significant signs may be gathered under systemic headings.

TABLE 10.—PHYSICAL FINDINGS—SKIN AND RELATED STRUCTURES.

	No.	%.
Petechiæ: Skin	53	60.2
Splinter hemorrhages	3	3.4
Mucous membranes	13	14.7
Retina	10	11.3
Pallor (7 were café au lait)	24	27.2
Jaundice	8	9.0
Sweat, profuse	6	6.8
Subcutaneous nodule	5	5.6
Macules	4	4.5
Gangrene	4	4.5

The high incidence of skin petechiæ (60.2%) was not unexpected. The favorite sites were on the fingers or toes, in the webs of the same, and behind the ears. Subungual (splinter) hemorrhages were infrequent in this series. No rule can be applied for the occasional earlier appearance of the petechiæ in the conjunctiva and the mucous membranes of the mouth. Indeed, in three instances the retina was the first site of the petechial eruption. The remarked pallor partook of a classical café au lait tint in the minority of these patients and subcutaneous nodules were uncommon. Gangrene of the skin is a startling but uncommon manifestation of this disease (Fig. 1).

TABLE 11.—PHYSICAL FINDINGS—HEAD AND NECK.

	No.	%.
Eyes: Lagophthalmos	3	3.4
Exophthalmos	2	2.2
Choked disks	2	2.2
Exudate	3	3.4
Embolism—central retinal artery	1	1.1
Ptosis	1	1.1
Neck: Carotid thrill	2	2.2

Table 11 demands no especial discussion save for the striking picture that was presented by the embolism of the retinal artery. The infrequency of choked disks and serious retinal changes is an indirect brief for the position that the uremia of endocarditis lenta must depend upon renal changes other than embolism.



FIG. 1.—Gangrene of the tip of the nose resulting from embolism of nasal branches of the facial artery in *S. viridans* endocarditis lenta.

TABLE 12.—PHYSICAL FINDINGS—CARDIOVASCULAR SYSTEM.

	No.	%.
Heart:		
Thrill:		
Apical—Systolic	28	31.8
Presystolic	27	30.6
Enlargement	62	70.4
Murmurs:		
Mitral—Double	49	55.6
Systolic	23	26.1
Presystolic	6	6.8
Aortic—Double	12	13.6
Systolic	13	14.7
Diastolic	14	15.9
Pulmonic—Systolic	1	1.1
Pericarditic friction	5	5.6
Arrhythmia:		
Auricular fibrillation	5	5.6
Complete heart block	1	1.1
Peripheral circulation:		
Edema	20	22.7
Arterial hypotension	17	19.3
Arterial hypertension	3	3.4
Vasomotor instability	1	1.1
Dicrotic pulse	2	2.2
Centrifugal venous pulse	10	11.3
Aneurysm, ulnar artery	1	1.1

The cardiovascular findings are among the most important in endocarditis lenta. As anticipated the mitral murmurs overwhelmingly predominated. Cardiac enlargement was a very common finding (70.4%). Edema and arterial hypotension were further

evidences of myocardial weakness. The positive centrifugal venous pulse reflected the same situation in the presence of relative tricuspid insufficiency.

TABLE 13.—PHYSICAL FINDINGS—LUNGS AND PLEURA.

	No.	%.
Chronic passive congestion	21	23.8
Bronchopneumonia	18	20.4
Pleuritic friction	9	10.2
Pleural effusion	5	5.6

As previously indicated, the evidences of congestive heart failure occurred with surprising frequency. Of this group 23.8% showed chronic passive congestion of the lungs. In most instances the bronchopneumonia was a terminal manifestation. The pleuritic reactions were in response to infection and infarction.

TABLE 14.—PHYSICAL FINDINGS—ABDOMEN.

	No.	%.
Abdominal tenderness: Right upper quadrant	4	4.5
Left upper quadrant	4	4.5
Muscle spasm	7	7.9
Enlarged liver (chronic passive congestion)	38	43.1
Palpable spleen	62	70.4
Perisplenic friction	3	3.4

Especially interesting in Table 14 are the high frequencies of hepatomegaly and splenomegaly, 43.1 and 70.4%, respectively. In the case of the enlarged liver, chronic passive congestion played the important rôle. Splenomegaly is a recognized clinical feature of endocarditis lenta and the high percentage of palpably enlarged spleens gives increased diagnostic importance to this finding. Perisplenic friction rubs were infrequent but interesting findings.

The following case presents some of the diagnostic difficulties in the abdominal manifestations of *S. viridans* endocarditis lenta.

CASE 3.—E. P., white male, aged 13, complained of pain in the right groin. Weakness and general malaise initiated the present illness 2 months previously. He also experienced slight headaches, burning on urination and the passage of dark-colored urine for a few days. The general malaise and disability advanced considerably in the first 2 weeks of the illness and edema of the legs appeared about a week and a half after the onset. This swelling was greater in the calf and posterior aspect of the thigh and more marked on the right than the left. Chills and fever became pronounced about 2 weeks before admission. A week and a half previous to admission pain of a steady order developed in the right groin. Exacerbations with intervals of complete remission occurred from time to time. Occasionally there was a radiation along Poupart's ligament. There was some pain in the sacral region. A weight loss of 17 pounds had occurred during the present illness. The past medical history was irrelevant.

On physical examination the following pertinent details were established: Pronounced pallor, spasm of both abdominal recti, tenderness over the right renal and the right inguinal regions. Shortly thereafter marked rebound tenderness appeared over the right lower quadrant of the abdomen. The appearance of a double mitral murmur led to the suggestion of an endocar-

ditis and the deferment of the surgical exploration of the suspected abdominal inflammatory process.

The laboratory examinations were significant in the presence of a hypochromic anemia, the hemoglobin ranging from 42 to 45% and the erythrocytes from 3,690,000 to 3,970,000. Leukocytoses of 13,250 with 86% neutrophils and 19,750 with 83% neutrophils obtained. Blood cultures were negative.

The temperature ranged from 99° to 102.8° F. and on the sixth day after admission there was a cerebral accident with advancing evidences of left-sided hemiplegia. A lumbar puncture was done; the cerebro-spinal fluid showed 85 cells per c.mm., 80% of which were small lymphocytes. The following day a cisternal puncture was done and the cells in the obtained fluid numbered 36 per c.mm. There was a rise in the mid-zone of the gold sol curve.

The patient died on the tenth day and at necropsy the typical vegetations of endocarditis lenta were found on the mitral valve, extensive infarction of the left kidney and spleen was determined and there was an embolus in the right common iliac artery with an abscess in the tissue adjacent to the same. A basal meningitis completed the pathologic findings.

TABLE 15.—PHYSICAL FINDINGS—NERVOUS SYSTEM.

	No.	%.
Meningitic signs	8	9.0
Cerebral embolic signs	7	7.9
Hemiplegia	10	11.3
Facial palsy	1	1.1
Motor aphasia	1	1.1
Horner's syndrome	1	1.1
Convulsions	1	1.1
Choreiform movements	1	1.1
Fibrillary tremors	1	1.1
Stupor	3	3.4

The embolic and meningitic data in Table 15 are clearly explicable on the basis of the pathologic changes of *S. viridans* endocarditis lenta. By the same token the incidence of hemiplegia (11.3%) might well be expected, although it would seem a rather high figure.

The following case report portrays certain unusual neurologic manifestations of this form of endocarditis.

CASE 4.—E. H., white female, aged 18, complained of weakness with recent loss of vision. She dated the onset of her trouble at 6 months previously when she had first noted palpitation with some precordial pain. Dyspnea had appeared on exertion and she had become so weak that for 4 or 5 months she had been unable to work. For the past month there had been some loss of vision. The visual disturbance had progressed rather rapidly so that she could distinguish only moderately large type. Upon admission the patient vomited. An attack of rheumatic fever had occurred 10 years previously.

Significant among the physical findings at the time of admission were the retinal changes of bilateral choking of the disks, narrowing of the arteries, engorgement and tortuosity of the veins, fresh hemorrhages near the disks. The cardiac findings included a systolic thrill at the apex, cardiac enlargement, apical and basal systolic murmurs. The spleen was palpably enlarged. The diagnosis of endocarditis lenta was confirmed by a positive blood culture for streptococci whose order could not be established antemortem.

Four days after admission the patient became stuporous and the neck rigid. Edema of the right side of the face with bilateral ptosis developed. The extrinsic muscles of the right eye were paralyzed, the right pupil dilated, the tongue deviated to the right, the right arm increased in tone with reduced grip in the right hand. The Kernig sign was positive. All deep tendon reflexes on the right were increased over those on the left. There was a bilateral positive Babinski sign. Some tenderness was remarked over the ribs. Lumbar puncture obtained a xanthochromic spinal fluid. A diagnosis of aneurysm of a vessel of the circle of Willis with leakage was made by Dr. Mabel G. Masten. A cisternal puncture 2 days later withdrew almost pure blood. The fluid obtained upon lumbar puncture subsequently was slightly less bloody. The further course was one of progressive decline to death 6 days after the described episode.

At *necropsy* subacute bacterial vegetations were found upon the mitral valve and upon the mural endocardium of the left auricle. There was infarction of the spleen and kidneys, and a fresh blood clot was found about the pons and the medulla and as far forward as the optic chiasm. There was a fresh clot in each of the lateral ventricles. After fixation a highly cellular inflammatory exudate was found in the wall of the basilar artery which was partly destroyed and greatly dilated. An infected infiltration of the surrounding brain tissue was defined. A ruptured mycotic aneurysm of the basilar artery was diagnosed. The infarcts in the spleen and kidneys proved to be infected.

TABLE 16.—PHYSICAL FINDINGS—EXTREMITIES.

	No.	%.
Clubbed fingers	19	21.5
Emboli	5	5.6
Joint involvement	5	5.6
Tremor	2	2.2
Bone tenderness	1	1.1
Quadriceps weakness	1	1.1

Of particular interest were the lower incidences of clubbed fingers and of bone tenderness than ordinarily given. While clubbing of the fingers may be a heritage of the congenital or the chronic valvular lesions of the heart, it is not uncommon to observe its independent development and progression in the course of *S. viridans* endocarditis lenta.

Case 5 illustrates infrequent lesions of this disease.

CASE 5.—E. F., white male, aged 18, presented a clinical picture of *S. viridans* endocarditis lenta upon the basis of a rheumatic involvement of the mitral and aortic valves, that had been first recognized 6 years previously.

Particularly interesting is the development of the complicating pain in the right arm which had suddenly appeared 2 weeks previously and after a month of the febrile course of the complicating endocarditis. Shortly after the onset of a sharp pain in the right forearm there had been a gradual swelling. The pain upon admission was aching in character and it decreased upon the direct application of heat.

The local examination of the right forearm disclosed a pulsating swelling which was exquisitely tender upon palpation. A presystolic bruit was heard over this swelling. Extension of the forearm and of the fingers greatly increased the pain. Pressure over the brachial artery, sufficient to obliterate the radial pulse, completely relieved the pain and caused disappearance of the pulsation and bruit.

Under local anesthesia a linear incision was made in the right forearm and an aneurysmal varix of the ulnar artery and vein disclosed. This was resected. Embolic phenomena dominated the subsequent course. Death resulted from cerebral embolism.

The laboratory findings in this group of patients were very interesting. Anemias of grave degree were unusual, only 5 patients (5.6%) registering erythrocyte counts below 2 millions. Levels of 2 to 3 millions were reached by 17 (19.3%) and 3 to 4 millions by 34 patients (38.6%). Thus it would appear that almost two-thirds of the patients of this group (63.5%) suffered from varying grades of anemia; but the majority of these might properly be classified as mild. The average minimal leukocyte count for 77 subjects was 10,880 and the average maximal for the same group 23,060. The lowest leukocyte count was 2950 and the highest 61,500. Forty-nine of 76 minimal counts (64.4%) ranged from 6000 to 12,000. The spread of the maximal counts for the 83 individuals with available data was much wider. Of 83 maximal counts 63 (75.9%) ranged from 10,000 to 28,000. Unfortunately, the differential leukocyte counts afford no critical information. The neutrophils averaged 80.4% in the minimal counts and 85.4% in the maximal.

Albuminuria was established 59 times (68%), while casts were found 56 times (63.6%). In 43 instances (48.8%) red blood cells were reported in the urine. The suggestion of the greater responsibility of an independent glomerular nephritis over focal embolic nephritis for renal insufficiency will be analyzed on a clinico-pathologic basis. Suffice it for the present to state that in 19 instances the non-protein nitrogen level in the blood exceeded 40 mg. %, but in only 3 of this number was the level over 120 mg. %. The renal form of endocarditis lenta is none the less a serious diagnostic and clinical problem, as witnesses the following example:

CASE 6.—P. F., white male, aged 29, complained of weakness and chills. His present illness dated to 6 months previously when he had gone to bed because of his chills and fever. Chills recurred weekly and weakness progressed apace. From time to time in the intervening period he had sat up but the chills continued until a month before admission. Sweats had been quite debilitating. The inventory by systems added only anorexia, urinary frequency, urgency and nocturia. A weight loss of 65 pounds had been observed in the past 9 months. The past medical history was irrelevant. The social history added only the excessive alcoholic habit.

To physical examination the important findings were the retinal changes of albuminuric retinitis, hypertrophied tonsils, basal congestive râles, cardiac enlargement with an apical systolic murmur, hepatic engorgement, palpable spleen and kidneys, blood pressure 126/72, and marked generalized anasarca. The urinalysis was particularly significant in the albuminuria with occasional hyaline and granular casts, many leukocytes and erythrocytes. The blood count on admission was 15% hemoglobin, 1,640,000 erythrocytes, 8400 leukocytes with 83% neutrophils and 17% lymphocytes. The non-protein nitrogen rose from 136 mg. % to 187 mg. % in the 9 days of hospitalization. The blood culture was returned positive for streptococci.

The patient died in uremic coma and at necropsy there were multiple vegetations on the tricuspid valve and on the wall of the right auricle. Aside from other findings the kidneys showed a granular injected surface with focal glomerulitis, marked arteriosclerosis and moderate interstitial connective tissue increase. There was a moderate amount of hemorrhage in the tubules which were distended with an albuminous material and a slight cellular exudate. The glomerular involvement was of an acute order.

The results of blood cultures are listed in Table 17.

TABLE 17.—BLOOD CULTURES.

	No.	%.
<i>S. viridans</i>	51	57.9
Streptococcus (type undetermined)	11	12.5
Diplococcus	2	2.2
Staphylococcus (type undetermined)	1	1.1
Staphylococcus and streptococcus	1	1.1
Negative (1 to 6 times)	12	13.6
None taken	9	10.2
Taken but not recorded	1	1.1

The experience in this relation closely paralleled the literature on the subject. The percentage figures, of course, relate to the total series and would thereby tend to minimize the overwhelming preponderance of the *S. viridans* responsibility for endocarditis lenta. This figure has been further distorted by the rather high percentage of undetermined streptococci in the blood cultures. A majority of these cultures disclosed growths within 72 hours. The ranges were 18 hours to 14 days.

A further laboratory observation warrants passing attention. The studies of Gessler² indicated an elevation of the basal metabolic rate even in the afebrile periods of this disease. In 9 instances of this series this observation has been confirmed and elevations as high as +56% have been recorded. Lacking a lucid explanation of this phenomenon its importance lies in the diagnostic confusion that may attend the evidences of sympathetic imbalance in the presence of an elevated basal metabolic rate in this form of endocarditis.

The course of the disease follows no fixed rule, if this series be a criterion. While its lentor may be cited as a dominant feature, many patients show a more or less fulminant course. A study of the temperature charts available (80) disclosed maximal temperatures of more than 102° F. in 65 patients (81.1%), whereas minimal levels of less than 99° F. were recorded in 77 (96.2%). Diurnal variations of 4.1 to 8° F. occurred in 59 patients (70.3%). Singular clinical remissions appeared in the course of 15 subjects (17% of the complete series) while in the hospital. A startling sense of euphoria accompanied certain of the late remissions in the constitutional picture and in isolated instances closely anticipated the terminal decline. Indeed so striking was this occasional coincidence as to give the circumstance an ominous portent. Such episodes are not to be confused with the well defined afebrile, abacteriemic phases of

the disease. It is exceedingly difficult to fix the duration of the individual case of *S. viridans* endocarditis lenta. From careful histories the course was thought to have lasted 1 to 3 months in 17 (19.3%), 4 to 6 months in 18 (20.4%), and 7 to 9 months in 9 (10.2%). These figures leave an equal number of the total series (44), including the discharged patients, for whose course no approximate duration could be set.

Of this series 64 (72.7%) died in the hospital. The manner of their exodus is charted in Table 18. The percentage figures relate to this group alone, since it is impossible to fix the exact cause of death in the discharged patients.

TABLE 18.—MANNER OF DEATH.

	No.	%.
Gradual decline	20	31.9
Congestive failure	20	31.9
Cerebral accident	11	17.1
Bronchopneumonia	8	12.5
Uremia	3	4.6
Miscellaneous	2	3.1

Note: Of this group, 3 had advanced cancer, 1 Paget's disease, 1 acute retention with hemorrhage and shock postoperatively, and 1 polycystic disease.

Congestive failure and general decline from toxemia are equally responsible for the ultimate fatal outcome according to the growing consensus. Uremia played a smaller rôle than was anticipated, but other complicating factors not uncommonly replaced renal insufficiency in the terminal picture.

Therapy was uniformly unavailing. A list of the inefficacious agents would serve no good purpose. Sodium cacodylate was the drug most frequently used. Transfusions were given in 30 subjects. One patient received a total of 29 transfusions without profit. Immuno-transfusions showed no advantage. Of the other procedures invoked, Roentgen therapy had the most extensive trial* (12 patients) and without evident effect.

Of the 64 patients dying of this disease in the Wisconsin General Hospital, 49 (76.5%) came to necropsy. These 49 postmortem cases occurred during a series of 2890 consecutive postmortems at this institution, an incidence of 1.7%. Since few figures are available on the incidence of *S. viridans* endocarditis lenta relative to the other types of endocarditis, a tabulation of all types as they occurred in this series has been made in Table 19.

The subacute lesions occurred twice as often as the acute ulcerative type, but only one-third as often as rheumatic endocarditis. Furthermore the true proportion of rheumatic involvement is not fully conveyed by the above table. In addition to the 155 cases

* This circumstance is explained by the fortunate experience of our associate, Dr. Chester M. Kurtz, in observing the recovery of a patient with *S. viridans* endocarditis lenta who received Roentgen therapy.

of rheumatic endocarditis, there were 57 cases of rheumatic heart disease wherein the valves were not grossly affected and 376 cases revealing on microscopic examination the perivascular fibrosis which, though not conclusive, is at least a presumptive sign of the rheumatic process. Since no duplication was made within these three groups, a total of 588 cases (20%) showed definite or presumptive evidence of rheumatic inflammation.

TABLE 19.—ENDOCARDITIS FOUND IN 2890 POSTMORTEMS.

	No. of cases.
Chronic endocarditis (marked distortion, thickening, calcification, etc.)	486
Rheumatic endocarditis (valvular only; acute, chronic, recurrent)	155
Acute indeterminate endocarditis (probably terminal)	76
Endocarditis lenta	49
Acute ulcerative endocarditis	24
Syphilitic (valvular, in addition to aortitis)	9
Cases with congenital cardiac lesions	16

The relationship of rheumatic endocarditis to *S. viridans* endocarditis lenta is not entirely clear. The portal of entry for the causative bacteria has not been definitely determined. It is well recognized that the findings at the postmortem table cannot give satisfactory evidence as to the route by which the valve becomes infected, whether from its own vessels or from the cardiac blood stream. Consequently, this phase of the subject has not been discussed. Yet in spite of the uncertainty clouding these etiologic factors, a generally satisfactory correlation can be made between the clinical expressions of this disease—signs, symptoms, course—and the morbid anatomy and processes disclosed at postmortem. The post-mortem findings may be readily divided into the primary cardiac lesions and the secondary extracardiac lesions.

CARDIAC LESIONS. *Valves.* *S. viridans* endocarditis lenta presents at postmortem a number of distinctive characteristics. (1) It is predominantly a disease of the left side of the heart, not only in its cardiac lesions proper but in the many remote extracardiac (embolic) lesions secondary thereto. As shown in Table 20 the mitral and aortic valves, either alone or together, were involved in 41 (83.6%) cases. With either the pulmonic or the tricuspid valve they were involved in 6 additional cases (3 of which were congenital heart cases). Only 2 cases accordingly involved the right side alone (Fig. 2). A single valve was affected in 30 cases, 2 valves in 17 cases, and 3 valves in 2 cases (both congenital hearts). (2) In this series, endocarditis lenta is not only predominantly a disease of the left side of the heart, but particularly of the mitral valve, which was involved, alone or in combination, in 40 cases. The aortic valve, alone or in combination, figured in 20 cases. (3) Through the distinctive tendency of the subacute vegetation to grow and proliferate rather than to ulcerate and destroy, it frequently encroaches

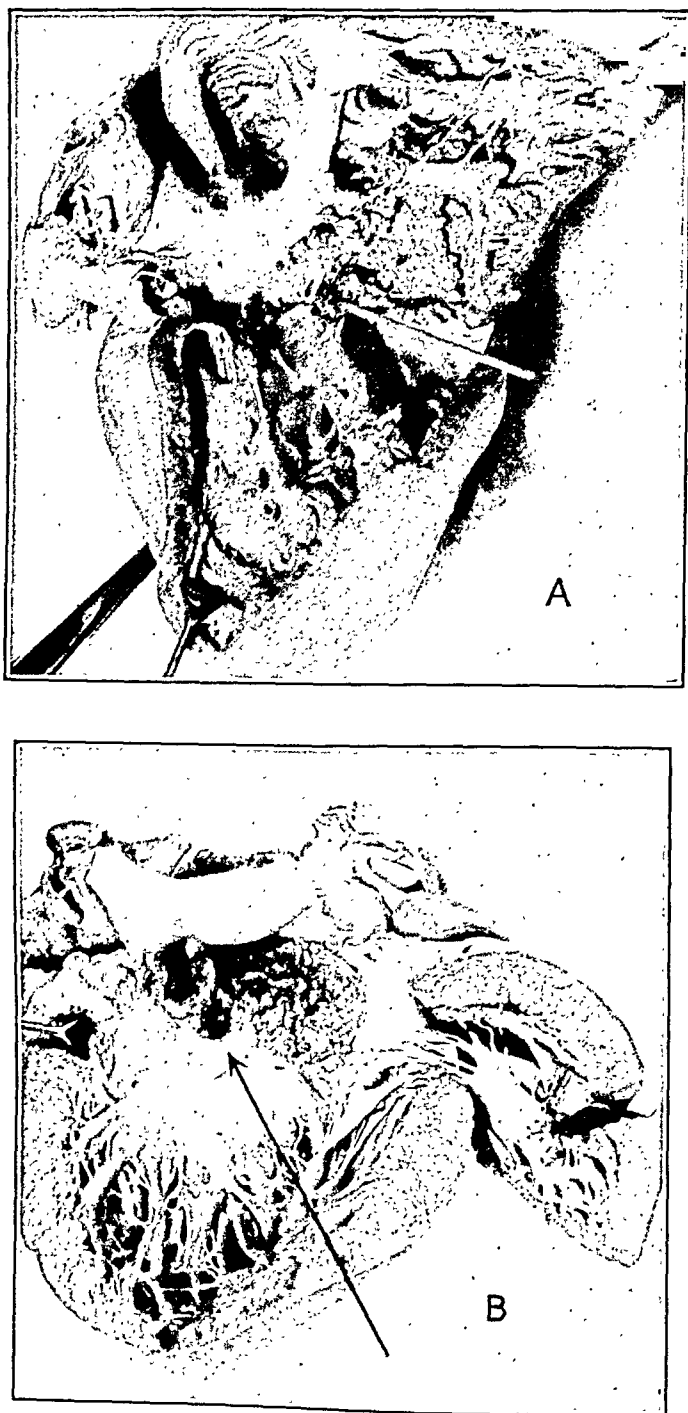


FIG. 2.—Characteristic vegetations of *S. viridans* endocarditis lenta complicating congenital heart disease: *A*, Chambers of the right heart opened, showing vegetations on the tricuspid valve, chordae tendineae and the mural endocardium. Probe extends through a congenital septal defect. *B*, Chambers of the left heart opened, showing massive, friable vegetations of the aortic valve extending to the ventricular surface of the aortic cusp of the mitral valve with much loss of its substance. Arrow points to septal defect. Weight of heart, 610 gm.

upon the chordæ tendinæ (where ulceration and rupture are not uncommon), upon the mural endocardium, and upon the intima of the pulmonary artery and aorta. Thirty-one cases (63.2%) showed involvement of these areas, distributed as follows: mural endocardium (with or without chordæ tendinæ) 24 cases, with the aorta 3 cases, with the pulmonary artery 1 case, and aorta alone 3 cases. One case, however, appeared to be primarily an involvement of the mural endocardium with extension onto the mitral valve. (4) Previously damaged or congenitally defective valves appear especially susceptible, if not actually indispensable, to the inception of this disease. There were 36 such cases (73.4% of the 49 cases coming to necropsy) divided as follows: congenital valvular defect, 6 cases (12.2%); sclerotic injury, 11 cases (22.4%); rheumatic injury, 19 cases (38.7%). Eleven additional cases showed rheumatic stigmata in the myocardium or pericardium although the valves grossly had appeared sufficiently normal so that no microscopic sections were taken. By including these 11 cases showing rheumatic involvement of the myocardium or pericardium, the total number of cases with rheumatic lesions regardless of heart area affected is brought to 30 (61.0%), and the total number of cases with congenital malformations or with previous injury, to 47 (95.7%). In one case an acute indeterminate endocarditis became superimposed upon the subacute lesion, the only instance in which the latter did not remain the ultimate process.

TABLE 20.—VALVES INVOLVED.

	No.	%.
Pulmonic alone	1	2.0
Tricuspid	1	2.0
Mitral	23	46.9
Aortic	5	10.2
Mitral and aortic	13	26.5
Mitral and tricuspid	1	2.0
Mitral and pulmonic (congenital heart)	1	2.0
Aortic and tricuspid	1	2.0
Aortic and pulmonic	1	2.0
Aortic and mitral and tricuspid (both congenital hearts)	2	4.0

 49

One case, a male aged 24, presented unmistakable evidence of a healed endocarditis lenta of the mitral valve, chordæ tendinæ, and auricular endocardium. The closest scrutiny of the history and post-mortem findings, however, failed to reveal any significant clue as to the mechanism of recovery.

Non-valvular. The principal postmortem lesions encountered in the myocardium, endocardium (other than vegetations) and pericardium have been arranged in Table 21.

The myocardium generally escapes serious damage throughout the major course of the disease. The 23 cases with underlying chronic interstitial fibrosis can be accounted for by the larger proportion of

middle aged and elderly patients in this series. As the disease approaches termination, decompensation not infrequently develops, as is indicated by the number of mechanical lesions listed in Table 22.

TABLE 21.—NON-VALVULAR CARDIAC LESIONS.

	No.	%.
Myocardium: Toxemia (fatty or parenchymatous degeneration)	8	16.3
Infarcts	7	14.2
Acute inflammation	5	10.2
Abscesses	2	4.0
Focal necroses	2	4.0
Chronic interstitial fibrosis	23	46.9
Rheumatic stigmata (without gross valvular involvement)	11	22.4
Endocardium: Mural thrombi—Left side	7	14.2
Right side	6	12.2
Both sides	1	2.0
Pericardium: Obliterated sac; universally adherent pericarditis	6	12.2
Acute or subacute inflammation	6	12.2
Petechial hemorrhages	12	24.4
Hydropericardium of various degrees	23	46.9

TABLE 22.—MECHANICAL LESIONS.

Chr. pass. congestion.	No.	%.	Excess fluid.	No.	%.
Liver	39	79.5	Chest	25	51.0
Lungs	35	71.4	Pericardium	23	46.9
Spleen	25	51.0	Abdomen	13	26.5
Kidneys	13	26.5	Subcutaneous	17	34.6

While at first glance the frequency of chronic passive congestion and excess fluid in the serous cavities and subcutaneous tissue would indicate myocardial incompetency as a very common condition, it should be stated that the former are postmortem (often only microscopic) findings.

The combination of damaged valves and myocardium with consequent changes in the blood current due to decompensation helps to account for the finding of uninfected mural thrombi, apart from vegetations, in 14 cases.

Hypertrophy of the heart seems to be the rule at least among males. Among 32 males, only 3 hearts weighed less than 380 gm., without a single instance of atrophy. The average weight was 535 gm., the largest heart reaching 1185 gm. Among 17 females, 7 hearts weighed less than 350 gm., there was one case of real atrophy, the average weight was 350 gm., and the largest heart weighed only 400 gm. Hypertrophy may be attributed to previous rheumatic or hypertensive disease, to the relatively prolonged course of the infection with time for cardiac adjustment, and to the low virulence of the causative bacteria, illustrating the pathologic axiom that a powerful toxin destroys but a mild toxin stimulates. The well recognized vulnerability of hypertrophied hearts to strain and infec-

tion is again exemplified. Cardiac dilatation occurred in one-half (24) of the cases.

Serious involvement of the coronary arteries was seldom seen. There were no cases of gross occlusion either by sclerosis or thrombosis, although microscopic examination disclosed 2 cases of thrombosis. It will be noted in Table 21 that 7 cases of myocardial infarction were found, all minute, however, and discovered only on microscopic examination. An ulcerated defect of the intima 0.8 by 0.5 cm. was found in the right coronary artery of one heart. Six cases, all over age 48, showed moderate or severe coronary sclerosis.

Serious involvement of the pericardium was likewise seldom seen. The number of cases of hydropericardium (23) appears rather large although in many instances it was of sub-clinical proportions.

EXTRACARDIAC LESIONS. Extracardiac lesions fall readily into two groups, embolic and non-embolic, or general. Lesions in both groups, however, are secondary to, and arise from, the primary cardiac lesions.

Embolic Group. Emboli or their consequences are common. They terminate in a wide variety of locations with a consequent wide range in effect. They provide many of the peculiar or distinguishing characteristics of this disease. The rather soft, friable, insecure vegetations furnish a constant potential source of supply. Since the vegetations were limited mainly to the valves of the left side, emboli were encountered generally in the systemic circulation. This circumstance is in contrast to the embolic phenomena of other cardiac conditions, chiefly arteriosclerotic or rheumatic heart disease with congestive failure, wherein the pulmonic circulation is more commonly affected. Of 648 cases of thrombosis (and emboli therefrom) tabulated from 2613 postmortems in the same series, 341 were found in the pulmonary artery.

The nature, frequency, and location of the embolic phenomena encountered are arranged in Table 23.

TABLE 23.—EMBOLI AND THEIR CONSEQUENCES.

Nature of lesions.	No.	Location.
Emboli (or thrombi)	18	Pulmonary artery, 5; coronary, 2; brachial, iliac, femoral, mesenteric, gastric, facial (nasal br.), basilar, renal, adrenal, post. tibial arteries, 1 each; multiple dissemination, 1.
Infarcts	82	Spleen, 37; kidney, 23; lung, 8; heart, 7; brain, 3; pancreas, 1; stomach, 1; testicle, 1; node, 1.
Gangrene	3	Nose, 1; foot, 1; heel, 1.
Petechial hemorrhages	44	Skin and mucous membranes, 28; serous membranes (mainly pericardium), 16.
Embolic pneumonia	3	
Embolic nephritis (Lohleins)	13	
Embolic(?) abscesses	8	Kidney, 4; heart, 2; node, 1; brain, 1.
Embolic(?) focal necroses	9	Liver, 4; heart, 2; spleen, 2; adrenal, 1.
Mycotic aneurysms	2	Basilar artery (with rupture), 1; mesenteric, 1.

Both cases of mycotic aneurysm occurred in young girls, aged 17 and 18, and within a week of each other. The case with the mycotic aneurysm (8 cm.) of the mesenteric artery had also developed a hemiplegia, but no brain examination was permitted at postmortem.

The scarcity of cerebral embolism and infarction, in all probability, is due to the small number of brain examinations allowed (5). The spleen and kidney are the organs most frequently involved. It is interesting to note that the liver, the largest organ on the systemic circulation, however, with a dual circulation, showed no infarcts and only 4 instances of focal necroses. Of the 82 instances of infarction listed, 29 were multiple in nature (more than one infarct in the same organ). Occasionally one infarct would be sterile, another infarct in the same organ, septic; they frequently showed variation in age. In contrast to the pyogenic embolic phenomena in acute ulcerative endocarditis, lack of suppuration is the rule here, although exceptions are not uncommon; 5 infarcts in the spleen, 4 in the kidney, 2 in the lungs, and 1 in the brain were septic—a total of 12 (14.6%). While *S. viridans* is an organism of low virulence, variation in tissue and individual resistance and in the number of organisms present in the detached vegetations probably explains the presence or absence of suppuration. Three instances of lung abscess occurring in conjunction with pneumonia or empyema were not considered to be of embolic origin. Venous (as distinct from arterial) thrombosis was noted 4 times, its scarcity again in contrast to its frequency in other types of heart disease where congestive failure prevails.

Non-embolic Group. Lesions produced by other causes are more general and less striking than those produced by emboli. They are mainly mechanical due to varying degrees of decompensation, or toxic or infectious due either to the primary or to a secondary infection. The principal mechanical lesions have already been tabulated in connection with the myocardial involvement (Table 22) and mention was made of the somewhat misleading impression they create, being not infrequently of a subclinical, terminal, or microscopic nature. The principal toxic or infectious lesions have been arranged in Table 24.

TABLE 24.—TOXIC AND INFECTIOUS LESIONS.

	No.	%.
Acute splenic tumor	30	61.2
Acute nephritis (other than embolic)	8	16.3
Bronchopneumonia (other than embolic)	27	55.2
Acute pleurisy (without pneumonia)	6	12.2
Widespread adherent perisplenitis	4	8.1
Acute lymphadenitis	18	36.7
Parenchymatous or fatty degeneration (toxemia):		
Heart	8	16.3
Liver	29	59.1
Kidney	21	42.8

The extent and degree of secondary anemia have already been set forth under the clinical discussion. It is to be noted that while the

disease involves only the heart in its initial stage, involvement of certain other organs invariably occurs. In this series, the spleen and kidneys were most frequently affected by emboli, the liver and lungs by toxic, infectious, or mechanical processes. The frequency of infarction in the spleen (37 cases) makes an interesting contrast to its complete absence in the liver in view of the fact that both the splenic and the hepatic artery spring from the celiac axis. The duality of the blood supply of the liver has been advanced in explanation without due respect to the analogous position of the lung where infarction is very common. The real extent of brain and meningeal involvement could not be ascertained in this series because of the limited number of brain examinations permitted.

The correlation of the clinical and the pathologic findings affords certain interesting information. With regard to cardiac involvement an antecedent history of rheumatic fever was elicited in 40.9% of the total group (88) and of the rheumatic chain just twice as frequently, 81.6%, whereas rheumatic lesions were demonstrable in 61.0% of the 49 subjects coming to necropsy. The history of a congenital cardiac lesion was elicited in 4 patients. Three of these patients came to necropsy with disclosure of congenital heart disease in every instance. Congenital defects confined solely to valves were disclosed in 3 additional cases. Cardiac enlargement was noted upon physical examination in 70.4% of the group as compared with the necropsy figure of 79.1%. Of the latter group, cardiac enlargement had escaped clinical recognition five times. From a clinical standpoint the subjective evidences of congestive failure encompassed a wide range from 47.7% of the total group showing dyspnea down to 23.8% with precordial distress. Turning to the physical findings, passive congestion of the lungs was established in 23.8% of the entire group and of the liver in 43.1%. Finally, from a clinical standpoint congestive failure was deemed responsible for 31.9% of the total deaths of this group in the hospital (64). At necropsy, chronic passive congestion of the lungs was remarked in 71.4% and of the liver in 79.1%. While no attempt is made to reconcile these obvious discrepancies between the clinical and the pathologic evidences of congestive heart failure, it should be noted that in many instances the changes upon death were demonstrable only to microscopy. Perhaps the most significant detail relates to the importance of congestive failure in fatal outcome of *S. viridans* endocarditis lenta by either method of analysis.

Splenic involvement by acute splenic tumor and infarction constitutes an important clinical feature of *S. viridans* endocarditis lenta. Fifteen patients (17%) suffered from left upper quadrant pain. Of this group, 8 came to necropsy and the spleen was invariably the seat of infarction. The spleen was palpable in 61 patients (70.4% of the general group) and in 28 of these the opportunity was afforded to weigh the spleen at necropsy. The average weight was

525 gm. All except one of the spleens recorded clinically as palpably enlarged exceeded the normal weight, and 23 of them (82.1%) weighed more than twice the normal figure (335 gm.). Among the remaining 17 subjects in whom the spleen was weighed but not palpated during life, only 5 were double the normal weight or larger. Two of the patients with pain in the left shoulder came to necropsy and both showed pleural involvement as well as splenic infarction.

Renal involvement in the form of infarction and nephritis also constitutes a very important clinical feature of this disease. Hematuria of a gross order was reported in 4 instances. Three of these subjects came to necropsy and infarction was demonstrated in all. Pain in the left flank was dependent upon renal infarction in the 2 isolated instances. It was the clinical conclusion that only 3 of the patients with a fatal outcome in the hospital had succumbed to uremia, although albuminuria, casts and red blood cells in the urine appeared in 68, 63.8 and 48.8% of the total group, respectively. A correlation of the non-protein nitrogen level in the blood and the lesions in the kidneys is afforded in Table 25.

TABLE 25.—CORRELATION OF BLOOD NON-PROTEIN NITROGEN AND RENAL LESIONS.

Non-protein nitrogen.	No.	Renal lesions.
40 to 60 mg. %	9	Parenchymatous degeneration and arteriosclerosis in 5 cases; infarct, 1; infarct with parenchymatous degeneration, 1; acute glomerular nephritis with multiple abscesses, 1; chronic glomerular nephritis, 1.
61 to 80 mg. %	4	Focal embolic nephritis in 2 cases; glomerular nephritis and arteriosclerosis, 1; subacute nephritis with septic infarcts and abscess and extensive arteriosclerosis, 1.
81 to 100 mg. %	1	Chronic urinary retention with hydro-ureter, bilateral ascending pyelitis, tubular degeneration and congestion and arteriosclerosis.
Over 120 mg. %	3	Focal embolic nephritis, 2 cases, 1 with hemorrhage in tubules and swelling of basement membrane, and the other with subacute diffuse nephritis and arteriosclerosis; acute glomerular nephritis, 1.

Focal embolic nephritis: 4 of above 17 cases—23.5%.

Focal embolic nephritis: 13 of total 49 cases (PM)—26.5%.

This analysis gives substantial support to the position that further renal injury than the focal embolic process of endocarditis lenta is the rule in patients who develop renal insufficiency in this condition. Glomerular nephritis is the most common contribution to this end. Serious renal involvement occurred in 40 of 49 subjects coming to necropsy (81.6%). Infarction occurred in 23; embolic nephritis, 13; acute suppurative nephritis, 4; acute glomerular nephritis, 6; subacute glomerular nephritis, 2; chronic glomerular nephritis, 2; sclerotic kidneys, 7. Obvious overlapping accounts for

excessive numbers, but at least the frequency and the importance of renal involvement are emphasized.

Bronchopneumonia was clinically determined in 20.4% of the group; but it was held responsible for the fatal termination in only 8 of the 64 dying in the hospital (12.5%). Since this figure was in striking contrast to the pathologic finding in this respect (55.1%), the group coming to necropsy was further analyzed. Of this series of 27 non-embolic bronchopneumonias, 13 had been so designated antemortem; 2 others had been termed bronchitis. The discrepancy is further reconciled in a measure by the fact that in 5 of the 27 recorded diagnoses at necropsy the lesions were microscopic. A sixth subject showed a small bronchopneumonic area of a tuberculous character.

Summary. Certain details in this clinico-pathologic analysis of 88 cases of *S. viridans* endocarditis lenta justify especial emphasis:

1. Further evidence is adduced to support the thesis of a close relationship between congenital and rheumatic lesions of the heart and endocarditis lenta.

2. Acute upper respiratory infections, rheumatic fever, infected abortion, dental extraction and massage for non-specific prostatitis apparently served as precipitating factors in the development of certain cases of this condition.

3. Contrary to the accepted opinion, congestive heart failure may attend or mask this condition.

4. The clinical manifestations and course of this affection are notoriously varied and inconstant. After the cardiac changes incident thereto, particular attention has been directed to its toxic and its embolic features. Splenic and renal changes, including embolism, were very frequent. Mycotic aneurysms offered serious diagnostic problems. Cerebral accidents were not infrequent. Occasionally a mycotic aneurysm of a cerebral vessel may explain certain neurologic phenomena of this condition. Again the clinical picture may suggest thyrotoxicosis, and the unexplained elevation of the basal metabolic rate may add to the diagnostic confusion.

5. This study offers material support to the importance of the diagnostic triad, *i. e.*, petechiæ, splenomegaly and a positive blood culture for the *S. viridans*. Given the background of a congenital or a rheumatic heart lesion and a remittent fever, this triad offers the logical direction of attack.

6. The prognosis of *S. viridans* endocarditis lenta is very grave. Only inferential evidence of the pace of the decline is offered by the circulatory, renal, embolic, toxic, constitutional and hematologic reactions. Although remissions of varying durations and degrees are the rule, certain of these patients undergo a rapidly progressive decline. Attention has been directed to the ominous significance of the euphoria that attends late remissions.

7. This group included one instance of healed endocarditis lenta.

The clinical activity apparently occurred at a period removed from the hospitalization. All therapy in the remaining number (87) was unavailing.

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THE OCCURRENCE OF CORONARY ARTERY THROMBOSIS IN POLYCYTHEMIA VERA.

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STUDENTS of polycythemia or of coronary artery thrombosis, as a rule, have ignored the problem of any interrelationship or have failed to comment on the infrequency with which both conditions are encountered in the same individual.

In a rapid and fairly complete survey of the literature of the past 20 years we have come upon the following references: Oppenheimer⁴ who reports 7 cases of vascular thrombosis. The clinical diagnosis of acute coronary occlusion was made in 1 of these cases, a male of 38 years, with a known history of polycythemia of 11 years' duration. The patient recovered.

Two other cases have appeared with autopsy findings. One of these was reported by Christian.² This was a male of 55 years, listed as Case 4, who revealed at autopsy multiple vascular thromboses of long standing. The brain, aorta, spleen, heart muscle and the coronary arteries were involved. There is no reference to any generalized arteriosclerotic state. Still another autopsied case is that published by Boyd.¹ It is an excellent example of the concurrence of polycythemia vera with coronary occlusion in a comparatively young male of 37 years. The heart weighed 325 gm. and the anterior wall of the left ventricle exhibited large scars; at the apex the muscle was quite thin and bulging. About 1.5 cm. from the mouth of the left coronary artery there was an occluding thrombus, the upper portion of which was organized and recanalized, the lower portion showed uniform fibrous thickening of the intima. The wall of the vessel was surprisingly free of atheromatous alteration and this was true of the other coronary vessels.

The combination is especially infrequent in the case of younger patients. Coronary artery sclerosis with thrombotic manifestations in older groups who show decrescent processes, hypertension,

perhaps involutionary vascular alterations associated with hypothyroidism, is not unusual; but with such a background a concurrent polycythemic state cannot be singled out as the sole or primary cause of thrombotic occlusion. In younger subjects with no intrinsic alteration in the walls of the blood-vessels the pathogenesis of polycythemia clearly appears to be related to the formation of coronary thrombosis and this relationship is of interest and significance.

The pathogenesis of polycythemia is not clearly established. It is quite likely, and this is a point of view developed by Lichtwitz, that important neurohormonal connections link the bone marrow and other hematopoietic structures to hypothalamic regulations. Be this as it may, the outstanding feature of polycythemia frequently is a profound increase in all the elements of the blood. The blood volume, viscosity, all the formed cellular elements, the minerals of which calcium is an example, proteins of which globulin is an instance, are greatly increased. This marked *hyperplasia* of the blood, as a rule, is a chronic feature.

Concomitant with this hyperplasia is a *sluggishness*, in some cases, a marked slowing of the blood current within small vessels, *i. e.*, the capillary-bed of various organs, notably the lungs. This retardation or stagnation of blood in these beds is associated with anoxemia, often the degree of anoxemia is close to the threshold of cyanosis. The anoxemia together with a reduced blood flow promote the formation of thrombi and the thrombi in turn lead to hyaline, eventually to arteriosclerotic, alterations in the walls of these small vessels. Good sized veins and good sized arteries fail to exhibit any effective degree of slowing of bloodflow unless congestive failure or some other cause for reduced blood flow intervenes.

Inasmuch as the hyperplasia of the blood is general, *i. e.*, throughout the cardiovascular system, and since especially in young individuals the vascular conduits are not so apt to be diseased, we are forced to recognize that a general tendency to thrombosis in polycythemia in younger individuals, at least, may be linked to some general hematologic cause. This is not to deny that the same forces may be at work in older individuals also. The tendency to thrombose has been ascribed to a hereditary somatic factor, "thrombophilia" (Libman³), but more specifically to the enormous rise in the number of blood platelets. However, blood will clot in the absence of blood platelets as in the case of fishes, birds, reptiles, and lymph also, containing as it does no platelets, clots. It has been argued that substances or ingredients of the platelets may be liberated into the blood fluid and are responsible for intravascular clotting, not only in these lower forms but in human blood as well. This line of reasoning, however, leaves out of count the fact that although arterial as well as venous blood contain increased quantities of platelets (and their ingredients in whatever form they may

exist), the incidence of venous thrombosis in this disease far exceeds that of intra-arterial clotting. Possibly the more powerful arterial stream renders it difficult for thrombi to form and to secure an anchorage in this side of the vascular tree, but this hypothesis remains unsupported by experimental evidence.

In polycythemia venous thromboses are frequent and these involve chiefly the limbs, the lung bed, and the large intra-abdominal veins. The veins of the extremities, especially the legs, often suffer phlebitic and other thrombotic manifestations, sometimes associated with arterial changes as in the case of thromboangiitis obliterans. A general picture of polycythemia, in the beginning probably of the relative type but merging eventually into the genuine form, is not rare in connection with thrombosis of the hepatic, portal, gastric, splenic or renal venous system. There are occasions when it is well nigh impossible to say whether the thrombotic lesion was secondary to the polycythemia or *vice versa*. But after all, this variation in sequence of events may not be a vital point when, as is the case here, the blood disease and the venous thromboses are closely related. A postponement of the appearance of the hematologic picture as after the occurrence of thrombosis may mean merely that there was a delay in the development of this one feature of the disease. The usual course is for thrombosis to ensue after the blood is already polycythemic but the existing underlying pathogenic process can operate to produce thrombosis even when the blood is greatly improved.

Thromboses in the lungs, or better in the lesser circulation, are frequently found in polycythemia. The thrombi are formed in the vast capillary bed, also in the smallest arterioles and even in medium sized vessels. The extensive capillary network with its reservoir function is a special site of predilection for variations in bloodflow and this region, also, is the chief and "optimal" area for the interchange of gases between the atmosphere and the blood. Disturbances in function of this interchange lead to anoxemia. Accordingly, it is not surprising to note that some degree of dysfunction of the lesser circulation, expressed as diminished oxygen saturation of the blood (anoxemia) and diminished bloodflow, coexists with many conditions or diseases associated with polycythemia, *i. e.*, congenital heart disease, long-standing mitral stenosis, emphysema, so-called primary types of pulmonary fibrosis, and states that induce a lowered oxygen tension of the blood as among dwellers at high altitudes.

The arterial vessels of the lungs carry venous, oxygen-unsaturated blood and the venous channels carry arterial, oxygen-saturated blood. Nevertheless, the occurrence of thrombosis is not more marked in the pulmonary arterial bed than in the pulmonary venous bed. This is due to the fact, we believe, that the rate of bloodflow probably differs little in the finer arterial and finer

venous vessels. Both sets of vessels, therefore, may be looked upon as one territory with a common incidence for thrombosis formation.

In polycythemia, arterial thromboses are comparatively infrequent. They are encountered in the limbs, especially the lower extremities. Even younger individuals sometimes exhibit obliterating arteriosclerotic endarteritic alterations and interestingly enough these vascular changes seldom lead to gangrene. The appearance of thromboangiitis obliterans in younger individuals who have polycythemia is not altogether "pure coincidence" and the same may be said for spasm, claudication, known to seize peripheral arteries. Thromboses in the arterial channels of the brain occur in polycythemia and may be unassociated with arteriosclerotic changes in the vascular wall. Thromboses in the arterial system of the lungs have been discussed already in connection with venous thrombosis in the lesser circulation.

We come now to thrombosis of the coronary vessels. While it is true that thrombosis in these channels is not frequent in polycythemia vera, it is not as rare as is generally believed and to this the following cases with autopsy records from the Montefiore Hospital bear witness. In all, 7 cases of polycythemia came to autopsy, and of these 3 (Cases 3, 4 and 5) had myocardial alterations with associated coronary occlusions; 2 (Cases 1 and 2) showed extensive, similar changes in the heart muscle but no thrombus in the coronary tributaries. The other 2 cases in the series were free of myocardial damage and of coronary thrombosis.

Case Abstracts. CASE 1.—M. S. (5099), a 50-year-old male with polycythemia vera (hemoglobin, 110 to 140%; red blood cells, 5,272,000). He had a thrombosis of the right internal saphenous vein and residual signs from a right hemiplegia of 6 years' duration before admission to the hospital. Although not clinically suspected, the electrocardiographic tracings suggested that he had had myocardial damage on the basis of coronary occlusion. The blood pressure was 134/90. He also had signs pointing to a duodenal ulcer.

The heart at autopsy weighed 330 gm. The apex of the left ventricle was the site of a healed infarct with aneurysmal dilatation and thrombus formation. The left side of the heart was dilated and hypertrophied. The coronary vessels contained very small atheromatous areas; nowhere was there any encroachment upon the caliber of the lumen. Neither the main branches nor offshoots showed any evidence of thrombosis; the anterior descending ramus was traced to the very apex of the heart and only an occasional small atheromatous area was uncovered.

CASE 2.—J. A. (5154), a 63-year-old white male, had had a paralysis of the right side 4 months before admission, with impairment of speech. Residual signs of this thrombosis (of the left lenticular striate artery) were still present and a note in the record called attention to the possibility that the thrombosis was related to his polycythemia vera. His hemoglobin was 128%, the red blood cells 8,100,000. He passed through an episode of acute cerebral thrombosis but no clinical features of sudden coronary

occlusion ever appeared. The electrocardiographic tracings revealed left ventricular preponderance. He died of a terminal pneumonia.

Autopsy disclosed thromboses of the veins of the suprarenals and the pituitary gland, also gastric erosions. The heart weighed 380 gm. and the left ventricle was hypertrophied. At the apex, the muscle was thinned and showed the evidence of myocardial infarction. The coronary vessels were moderately arteriosclerotic but there was no narrowing or occlusion. One large coronary vessel had microscopic initial thickening with the media uninvolved. There was hyaline fibrosis of the heart muscle.

CASE 3.—T. G. (5498), a 66-year-old white female, was known to have had polycythemia vera for at least a year before admission. At that time the right leg was ulcerated, later the left leg. The radial arteries were tortuous, the brachial arteries pulsated visibly, and the right dorsalis pedis had no palpable pulsation. The hemoglobin was 122% and the red blood cells were 8,700,000. The blood pressure was 122/96. She developed gangrene of the lower half of the left lower limb and ulceration and gangrene of the 3d, 4th and 5th toes on the right side. Clinical signs of an abrupt coronary occlusion were absent. She died of a terminal pneumonia.

Autopsy revealed an organized thrombus in the inferior vena cava partially occluding this vessel and a partially occluding thrombus in both iliac veins. The heart weighed 210 gm. The right coronary artery contained an organized thrombus 3 mm. beyond its ostium and extending downward for about 5 or 6 cm. The lumen of the vessel was entirely filled but the thrombus was recanalized. Peripheral to the occlusion the vessel was smooth with only an occasional small intimal fleck. The coronary vessels in general were tortuous but exhibited relatively little arteriosclerosis. The aorta and kidneys were arteriosclerotic.

CASE 4.—M. B. (6513), a 53-year-old white male, was known to have polycythemia vera at least 2 years before admission. At that time also, he had had an attack of paresthesia of the left hand. About 9 months later he developed paralysis of the right side of the body and difficulty in speech. The blood showed hemoglobin 140% and red blood cells 9,900,000. He developed a severe and sudden splenic infarct and later gangrene of the right toe. At no time was there any clinical ground for believing that he had had an occlusion of his coronary vessels. The blood pressure ranged from systolic 104 to 164 and diastolic 58 to 90.

Autopsy showed old thrombi in the branches of the splenic artery and old thrombi of the cerebral vessels. The heart weighed 320 gm., the left ventricle was hypertrophied and the heart muscle had many scars. The coronary vessels contained old thrombi that were canalized. The coronary vessels in general were patent and free of arteriosclerosis. There was a chronic hypertrophic gastritis.

CASE 5.—H. B. (7747), a 36-year-old white female, had known polycythemia of 5 years' duration. In March, 1938, her hemoglobin was 140% and the red blood cell count was 7,240,000. The blood pressure was 134/92 and her electrocardiographic tracings were normal. About a month later she developed an abrupt episode of what was diagnosed clinically as an acute coronary thrombosis. She became markedly dyspneic, orthopneic, cyanotic and the blood pressure could not be measured. Twelve days later signs of precordial oppression appeared and pain radiating into the left shoulder. She had a temperature of 101° F. and coughed blood-tinged sputum that led to the diagnosis of pulmonary infarction. Shortly before exitus her electrocardiographic tracings revealed signs of infarction of the anterior wall of the heart. She died about a fortnight after the onset of this acute attack.

Autopsy disclosed multiple infarctions of the lungs, multiple infarctions in the heart. The heart weighed 270 gm. The main stem of the left

coronary artery was occluded by a fresh red thrombus extending down along the entire course of the left anterior descending branch; the left circumflex coronary artery contained many thick eccentric arteriosclerotic plaques but no thrombi were seen.

A special caution is necessary in interpreting the autopsy findings in Cases 1 and 2. In both these patients the heart muscle was seriously compromised and resembled the damage usually associated with coronary artery occlusion. As a painstaking search of these hearts failed to disclose occlusion in any of the coronary vessels, the basis for the myocardial alteration remains obscure. Strictly speaking, these two cases do not belong in the series of examples of the coexistence of coronary occlusion and polycythemia vera. They have been included, however, in order to direct attention to the occurrence, in advanced polycythemia vera, of marked myocardial damage of the type *associated practically always* with coronary thrombosis.

Conclusions. Although there have been extensive investigations on the principles underlying the mechanism of blood clotting and on the formation and organization of thrombi, we are still unable to explain the precipitating cause of an intravascular clot. Nowhere is this truer than in connection with the coronary arteries, and this problem assumes a fresh interest in connection with an analysis of coronary thrombosis in polycythemia when these vessels remain unaltered. The cases we have described illustrate that the clinical manifestations of thrombosis in a normal coronary vessel are indistinguishable from those observed in thrombosis of arteriosclerotic coronaries. These clinical features range from complete silence, *e. g.*, few or no clinical signs at the time of the occurrence of the thrombosis as in some of our cases, to sudden and dramatic onset of shock, pain and so on, as observed in our last case. The sequelæ of disturbed cardiovascular hemodynamics and the evolution of anatomic alterations in the heart are not different for polycythemic patients who develop coronary thrombosis. Arteriosclerosis was absent, or at most minimal, in the coronary tributaries; in several instances, this complete or almost complete freedom of coronary sclerosis was in contrast to the general arteriosclerosis of other parts of the vascular system. The myocardial lesions were not limited to microscopic size but were gross and followed the occlusion of good-sized coronary vessels. The 5 cases in this series of 7 polycythemics examined at autopsy suggest that the concurrence of polycythemia vera with coronary thrombosis or with marked myocardial damage of the type associated with coronary thrombosis, is more frequent than we were wont to believe and that coronary thrombosis, as well as other arterial and venous thromboses, is not to be dissociated from the pathogenesis of polycythemia vera.

It is of some interest to direct attention to the clinical seizures

of precordial pain in polycythemic individuals in whom the coronary vessels are not occluded. The character and the mechanism of this manifestation may be akin to that observed, with and without intermittent claudication, in states of anemia. It has long been known that polycythemia or anemia may be responsible for many of the same clinical features and among them, we have reason to believe, precordial pain should be included.

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VOLUNTARY HYPERCIRCULATION.

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At least 9 reports^{3,7,9,11,15-19} have been published describing 15 persons who have been able to increase their pulse rate on demand. The present report deals with 2 who were able to increase their pulse rate and also to raise their blood pressure at will. This investigation was undertaken to throw some light upon the relationships between the various physiologic adjustments which accompany these phenomena.

Subjects. The one subject, "A. L.," was not aware of his ability to control his circulation, until he was attending a course of instruction in human physiology, when he announced his ability to increase his pulse rate. When a preliminary examination had verified this, he was questioned as to the mental processes involved, but was unable to elucidate them other than by comparison with some ordinary somatic movements such as raising an arm. This may be compared with the report of Hoskins' introspection.³ "It is *not* induced by thinking of appropriately stimulating conditions or situations. It is probably no more—and no less—mysterious than is, for example, the flexing of a biceps muscle. Introspectively the two procedures seem similar. One simply 'wills' the change, and it takes place." In contrast, Cameron¹⁶ reports introspectively the

processes by which he trained himself to associate a spontaneous physiologic response to a fear stimulus with the will to accelerate his heart.

The other subject, "A. B.," stated that he had been able to increase his heart rate for several years before he studied physiology. His procedure was as follows: he would make himself conscious of his heart, either by feeling the pulse or the apex beat, by leaning his ear on a pillow or by any other of the common means familiar to us all. He would then attempt to anticipate each heart beat, or, as he said, "to pace his heart," and thus by what he termed "a sustained mental effort" applied before each beat, he was able to maintain an increased heart rate. In neither case was the subject aware of any emotional component either in the production of acceleration or in the process by which he learned to produce it.

For the more detailed investigation of this phenomenon, the following experiment was repeated 4 times, that is, twice for each subject.

Experimental Procedure. The subjects reported to the laboratory under basal conditions for the experiments. After 30 minutes' rest in the supine posture, 3 8-minute determinations were made of the basal metabolism. A half mask was used and the determination made by the Tissot open-circuit method with gas analyses by the Boothby-Sandiford² modification of the Haldane technique. At the beginning of the rest period a blood pressure cuff was fastened to the left upper arm. With this the technician made 5 auscultatory readings of systolic and diastolic blood pressures during the rest period and in between the basal determinations, and a pair of readings every half minute during the subsequent procedure. After the basal data had been collected, a second blood pressure cuff was attached to the left ankle. This was connected to an ink-writing tambour and inflated to 50 mm. Hg to record the pulse on a polygraph. The expiratory hose from the mask was then connected to one of a pair of 9-liter Tissot spirometers, so connected that when one filled it operated a relay-driven valve switching the expired air into the other spirometer. In this way a *continuous collection* of expired air was made. The duration of collection of each 9 liters of expired air was automatically recorded on the polygraph. A duplicate determination of the CO₂ and O₂ content was made on a sample from each of these collections of expired air. In some instances it was found convenient to pool several 9-liter collections, mix them and then obtain one sample. Respiratory frequency was determined from the polygraph record of a tambour actuated by the slight pressure changes within the mask.

Two to four 9-liter collections were made and the subject was then instructed to accelerate his heart. After a further 27 liters had been expired, he was asked to end the acceleration. Collection was continued for a further 10 minutes to observe the recovery period,* and immediately following this the subject was instructed to tense his arm and leg muscles. After tensing his muscles for a period corresponding to 27 liters' expiration, a final 10-minute period of observations was made and the experiment concluded.

The tensing of muscles was used as a control partly as a simple method of inducing a moderate metabolic increase and partly to test the suggestion of Carpenter, Hoskins, and Hitchcock³ that the tensing of skeletal muscles may be an essential part of the process of voluntary acceleration of the heart.

* One of the experiments was concluded at this point.

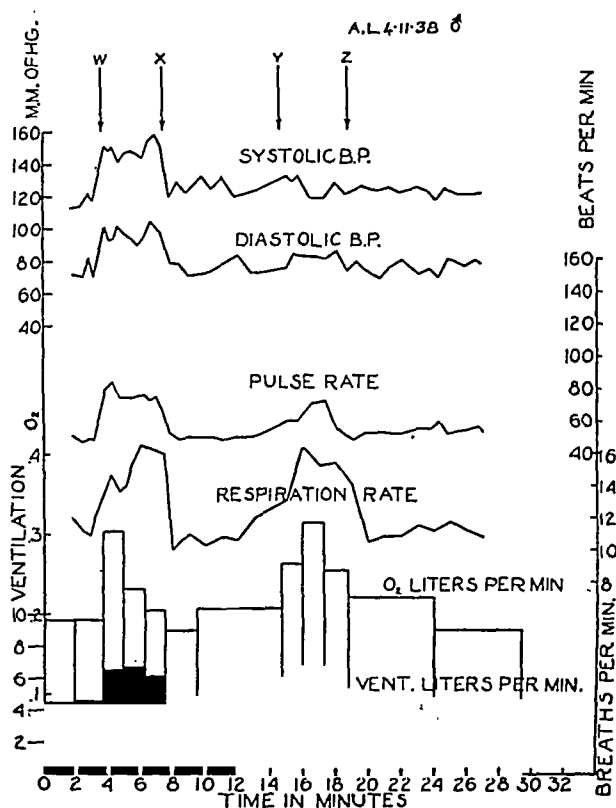


FIG. 1.—Increase of circulatory, respiratory, and metabolic functions on command (Subject "A. L.," 4/11/38). The upper 4 lines (systolic and diastolic blood pressure, pulse rate, and respiration rate) and the lower black histogram (respiration volume) are plots of the actual values measured. The upper (oxygen consumption) histogram is computed from the ventilation volumes and analyses of the expired air. The time blocks in the histograms indicate the duration of the collections of expired air. The pulse rate was counted for 6 seconds every half minute from a continuous polygraph record and was plotted in the middle of the interval so counted; the respiration rate, counted for the whole of each half minute, was plotted similarly. The blood pressure readings were made at approximately 30-second intervals and plotted at times at which they were taken as indicated by a foot-operated recording signal. The unavoidable difference in the methods of plotting results in a slight discrepancy in the actual time relations in the graph, but we do not believe that this affects the conclusion discussed in the text. *W* and *X* indicate the time at which the subject was commanded to accelerate and to stop accelerating the pulse rate. *Y* and *Z* indicate the time at which he was commanded to stop and start the muscle tensing. The "ventilation in liters per minute" and "oxygen consumption in liters per minute" are both plotted as histograms, and hence no temporal confusion results. The same method of plotting cannot be followed for the systolic and diastolic blood pressures or for the respiration rate. Since our readings are not instantaneous, but extend over a period of time, it is customary to plot data of this sort at the middle of the temporal interval rather than at the end. Hence, when the point just preceding the command "*W*" is connected with the measurement made immediately after the command is given, the impression is given that the rise precedes the command, which is not the case. The question as to whether the rise in respiratory rate began before, simultaneously with, or after the blood pressure rise, can be answered only partially by critical examination of the plot. Our experimental method provided us with continuous measurements of pulse rate and respiration rate, but our measurements of blood pressure are necessarily made at specified temporal intervals. Our first blood pressure measurement after the command, occurred between 20 and 30 seconds after the order was given. Furthermore, irregularities in respiration make it extremely hazardous to draw conclusions about the speed at which the respiratory rate may change.

Blood Pressure and Pulse Rate. Figures 1, 2, 3, and 4 show the data from these experiments plotted against time. In the first place, it will be noted that in the subject (A. L., Figs. 1 and 2) to whom the procedure appeared effortless, the new frequency was well maintained, and the return to normal was abrupt in both experiments. In the other subject (A.B., Figs. 3 and 4) the building up of a high frequency was somewhat delayed; he was not completely successful in maintaining the high rate, and at the end of the effort the normal rate reappeared more gradually. In each case the systolic

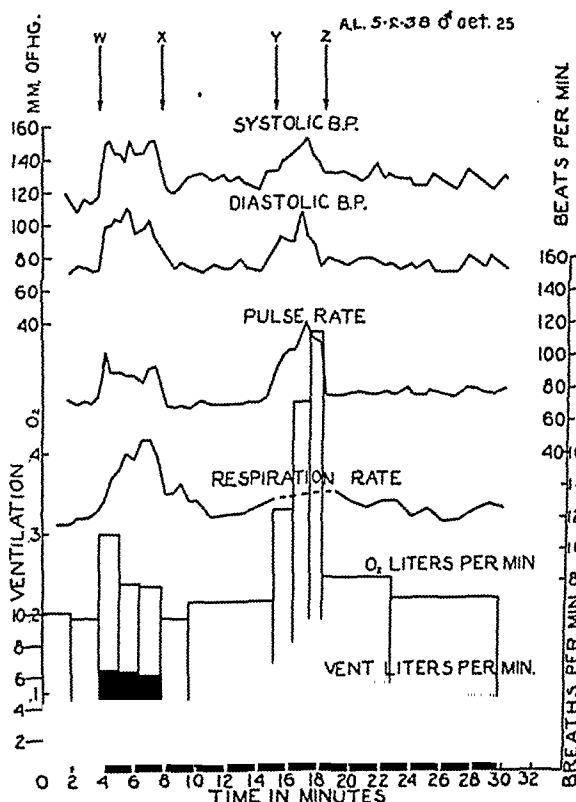


FIG. 2.—Increase of circulatory, respiratory, and metabolic functions on command (Subject "A. L.," 5/2/38). (See legend to Fig. 1.) Note the increase in circulatory functions on tensing muscles and the very great metabolic cost of this.

blood pressure also increased considerably. As to the diastolic pressure, the subjects differ in that "A.L." induces a clear increase, whereas "A.B." shows no change in one experiment (Fig. 4) and a barely recognizable rise in the other. In either case, however, the marked increase in pulse rate without corresponding drop in pulse pressure would be interpreted by many investigators (Read and Barnett;¹³ Liljestrand and Zander¹⁰) as evidence for an increased cardiac output. As to whether these subjects really showed an increased cardiac output, we have at present no direct evidence.

Toward the end of the experiment in each case the subjects' hands broke out into a cold sweat, and although we were unable to recognize any change with a skin resistance thermometer, this feeling of coldness suggests that in our subjects the blood flow through the limbs was diminished, as was shown to be the case by Taylor and Cameron¹⁶ using calorimetry, and by Tarchanoff¹⁵ and Pease¹¹ using plethysmographs. In this connection it may be noted that the slight drop in level of the pulse record which appeared every time (see Fig. 5) may be regarded as an indication of diminished limb volume and vasoconstriction.

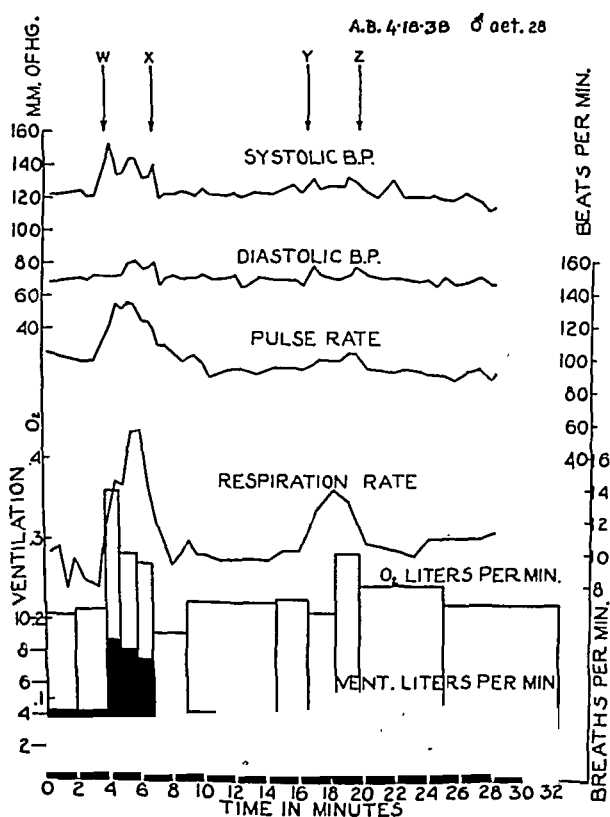


FIG. 3.—Increase of circulatory, respiratory, and metabolic functions on command (Subject "A. B.," 4/18/38). (See legend to Fig. 1.)

Increased Metabolism and Respiration. Our observations may be divided into 7 periods, each separated by rest or recovery periods. Four of these (*i. e.*, 1 on each of 2 days for each subject) were periods during which the subject was attempting to accelerate his heart. These are the "experimental" periods. The 3 remaining or "control" periods, 2 for "A.L." and 1 for "A.B." were those in which the subjects were tensing their skeletal muscles and not making any attempt at cardiac acceleration.

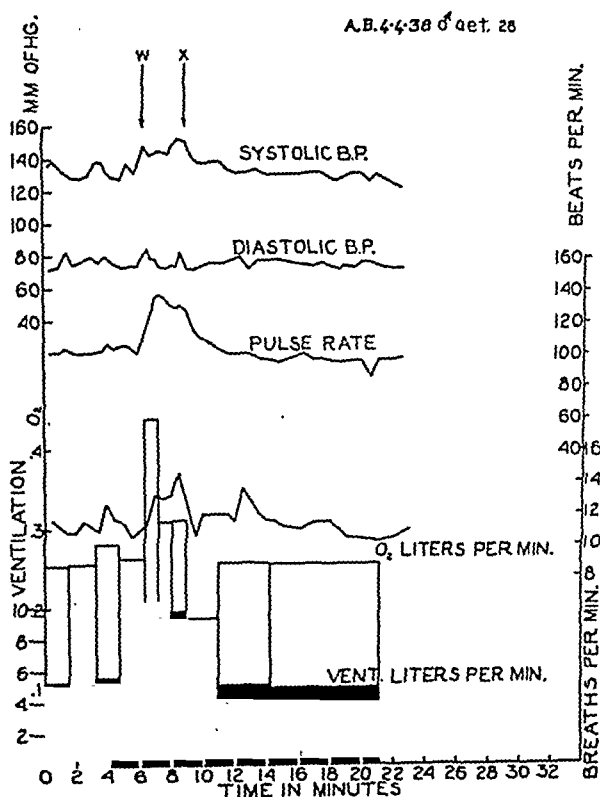


FIG. 4.—Increase of circulatory, respiratory, and metabolic functions on command (Subject "A. B.," 4/4/38). (See legend to Fig. 1.) This experiment was concluded without any muscle tensing control.

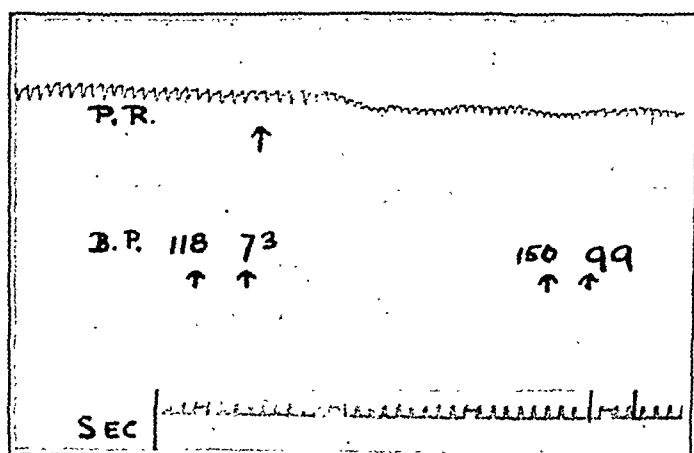


FIG. 5.—Part of polygraph record, showing the rapidity of onset of increase of pulse rate and blood pressure (Subject "A. L.," 5/2/38). Top line = record of changes in limb volume from cuff on ankle inflated to 50 mm. Hg. Arrow indicates command to increase heart rate. Second line = systolic and diastolic blood pressure. Arrows indicate moments of reading. Third line = time in seconds.

In each of the 7 periods, experimental and control alike, we find that there is an increase in respiratory frequency and volume of air breathed per minute, and a slight increase in oxygen consumption. In 6 of these periods the gas analyses (of which Table 1 is a sample) were characteristic of mild exercise. That is to say, the increase was found in both oxygen intake (Column 4, Table 1) and carbon dioxide elimination (Column 6, Table 1) with the respiratory quotient* (Column 7, Table 1) rising towards unity (in 1 case, "A.B.," 4/4/38, to 1.09). That a true increase in metabolism, probably due in part to increased work, was taking place is further shown by the fact that for each of the seven instances there is a clear-cut excess oxygen utilization if the oxygen intake for the periods of increase and the subsequent recovery periods be added and compared with the rate for the immediately preceding period (Table 2).

TABLE 1.—EXPIRED AIR ANALYSIS.

Experiment No. 2.		A. L.		April 11, 1938.			
Time for collection of 9.19 liters expired air, minutes. (1)	Expired air.		Apparent oxygen consumption.		CO ₂ elimination, liters per minute. (6)	R. Q. (7)	
	% O ₂ . (2)	% CO ₂ . (3)	Liters per minute. (4)	% of basal. (5)			
<i>Resting.</i>							
1.85	16.88	3.03	.194	91	.136	.702	
1.82	16.91	3.17	.193	91	.144	.746	
<i>Voluntary Acceleration.</i>							
1.28	16.48	3.61	.304	143	.235	.773	
1.25	17.45	3.41	.232	109	.226	.974	
1.36	17.63	3.17	.204	96	.194	.951	
<i>Resting.</i>							
1.91	16.95	3.53	.178	84	.153	.860	
5.18†	16.83	3.37	.206	97	.162	.786	
<i>Muscle Tensing.</i>							
1.37	16.85	3.31	.261	123	.201	.770	
1.23	16.55	3.44	.313	148	.232	.741	
1.55	16.46	3.52	.253	119	.189	.747	
<i>Resting.</i>							
5.24†	16.54	3.54	.219	103	.168	.767	
5.33†	17.22	3.15	.180	85	.147	.817	
† 25.57 liters.							

† 25.57 liters.

Hyperventilation. Whenever the voluntary acceleration was induced, we found evidence of hyperventilation (Taylor and Cameron;¹⁶ Carpenter, Hoskins and Hitchcock³) in addition to the increased work. The evidence for this appears in the gas analyses (Table 1), where the carbon dioxide content (Column 3) and the oxygen con-

* The term "respiratory quotient" is here used, as it was originally, to signify the ratio of carbon dioxide to oxygen in the expired air. It is not intended to include in the term any interpretation as to chemical processes occurring in the blood stream or in the tissues.

tent (Column 2) of the expired air are found to be high during the period of voluntary acceleration. This change is responsible to some extent for the R. Q. (Table 1, Column 7; and Table 2) which is noticeably higher during acceleration than during muscle tensing. The falling carbon dioxide content of expired air during the latter two-thirds of the voluntary acceleration (from 3.6% to 3.17%), in contrast to the rising concentration of carbon dioxide in the expired air during muscle tensing (3.31% to 3.52%) is further evidence that hyperventilation occurs in the former case. It may be seen clearly from the figures that the increase in ventilation has an abrupt onset and is maintained with very little change up to the end of the experimental period, whereas the increase in oxygen retention is much greater in the first than in subsequent periods. With hyperventilation the composition of the air in the chest tends to approximate more closely that of atmospheric air and the oxygen involved in this change gives a spurious appearance of a greater increase in oxygen consumption during the first periods than is real. At the end of the experiment the respiration abruptly returns to its previous level and the reverse change takes place. During this time the excess oxygen in the lungs is absorbed for metabolic use without appearing as oxygen consumption in the analyses. Accordingly, the observed oxygen removal from the room shows a spurious drop during the early part of the recovery, a drop which has been used in Table 2 to neutralize the effect of spurious excess oxygen absorption. This drop is a further index of the existence of hyperventilation. These variations in apparent oxygen consumption have been considered in detail in experimental hyperventilation in persons with "effort syndrome" (Soley and Shock¹⁴).

TABLE 2.—EXCESS METABOLISM DURING ACCELERATION.

	Apparent O ₂ consumption for whole period (liters).		R. Q. (peak value).
	Measured.	Excess.	
A. L. 4/11/38			
*Rest	0.71	..	0.746
Acceleration	2.37	0.24	0.974
Muscle tensing	3.24	0.39	0.817
A. L. 5/2/38			
*Rest	0.74	..	0.719
Acceleration	2.55	0.32	0.901
Muscle tensing	3.99	1.11	0.805
A. B. 4/18/38			
*Rest	0.80	..	0.756
Acceleration	2.98	0.33	0.989
Muscle tensing	3.63	0.33	0.780

* The preliminary rest periods only. The periods labeled "acceleration" and "muscle tensing" include the following period of recovery (see figures).

The first experiment on A. B. (4/4/38) is omitted from this table. The interpretation of this experiment is similar to that of the others, but the somewhat different arrangement of the timing makes the figures confusing and not strictly comparable to those in this table. Values in Column 2 computed from measurements in Column 1 and duration of periods. (See Table 1, Column 1; and Figs. 1-4).

Although we have definite evidence that hyperventilation was present in all the experiments and in none of the controls, we are inclined to agree with Taylor and Cameron¹⁶ and with Carpenter, Hoskins and Hitchcock³ that it is merely incidental and not an essential part of the mechanism for acceleration, since in a series of experiments (in preparation for publication) in which subjects were made to hyperventilate (by 3- or 4-fold) no increase of pulse rate or systolic blood pressure was found. Soley and Shock¹⁴ found that hyperventilation *per se* appeared to increase the rate of oxygen consumption and also to produce cutaneous vasoconstriction and sweating. The hyperventilation, then, may contribute to an uncertain degree to these phenomena in our experiments, but almost certainly is not the cause of the changes in blood pressure and pulse rate.

Muscle Tensing. In view of the experiments in which Hoskins³ accelerated his heart by deliberate tensing of muscles, it becomes imperative to consider the possibility that muscle tensing may be the underlying factor responsible for the cardiac acceleration in the cases reported here. Considering first the case of "A.L." as observed on April 11, 1938 (Fig. 1), it may be seen that in the experiment and the control during acceleration and muscle tensing respectively the apparent increase in oxygen consumption is of the same order of magnitude. The circulatory functions, on the other hand, are decidedly more increased during the experimental than during the control period. In fact, the real excess oxygen utilization (Table 2) was greater in the control period than in the other and the pulse acceleration was less, while the increase in blood pressure during the muscle tensing period was negligible. In the other experiment (Fig. 2) on this subject, it is true that all the circulatory measurements of the experimental period were closely imitated during the muscle tensing period, but this was at very much greater metabolic cost. On the evidence of these two experiments, then, it seems that the circulatory changes were determined by something more than the necessity for satisfying a metabolic need created by muscle tensing. Just as the subject has been shown to be hyperventilating, so we may speak of him as independently "hypercirculating."

Cardiac Output. In view of the 60% and 40% increases in pulse rate and the simultaneous 20% and 10% increases in pulse pressure, it is very likely that there was a sudden increase in cardiac output. The evidences of peripheral vasoconstriction in such cases—cold, pale extremities—and in the instances where measurements have been made, diminution in limb volume (Tarchanoff¹⁵), and limb blood flow (Taylor and Cameron¹⁶), together with the dilatation of the pupil observed in our subjects suggests the possibility that the whole train of events may be due to a sudden liberation of epinephrine. Taylor and Cameron found their experiments to be followed by a glycosuria but failed to find the expected hyperglycemia—a failure which they very reasonably believe may be due to the timing

of their blood samples. On the other hand, with such a mechanism one might expect a delay of a quarter minute for the epinephrine to pass from the adrenal body to the peripheral resistance and the coronary system. One might also expect a measurable after-effect. In one at least of our subjects the onset and cessation of the acceleration were very considerable within 10 seconds of the command (Fig. 5).

Moreover, Euler and Liljestrand⁵ found that subcutaneous doses of epinephrine great enough almost to double the cardiac output produced no increase in diastolic pressure; in fact, in every case they show a very small decrease. Similar findings are reported by Elliot and Nuzum.⁴ Pickering and Kissin,¹² Gordon and Levitt,⁸ and Fatheree and Hines⁶ find similar effects with small doses intravenously though larger doses commonly produced a rise. Grollman explains the findings of Euler and Liljestrand by suggesting that in the dosage in question the vasodilator effects of epinephrine are greater than its vasoconstrictor effects to an extent sufficient to balance the increased cardiac output. It might be argued that we are dealing with a much larger liberation of epinephrine and consequently have a predominantly constrictor effect. Should this be so, it becomes necessary to consider whether the direct action of epinephrine on the heart can increase the cardiac output in the presence of a generalized vasoconstriction which must tend, by diminishing the *vis a tergo*, to lower the venous pressure and thus the filling of the heart.

Blood Mobilization. It would seem that the most likely way in which such a filling insufficiency could be compensated would be by the liberation of blood from the blood stores. Although such a liberation would in no way help to explain the rapidity of the phenomena, it would provide a possible explanation for the raised diastolic pressure. Let us then consider the possibility that such an increase could have been brought about in part by the rapid mobilization of some of the blood ordinarily stored in the cutaneous, splenic, mesenteric, and pulmonary vascular beds. With the exception of the last, these bloods are all venous, and in the case of the splenic, the most mobile store, of a very high oxygen capacity. The extra oxygen intake in the first minute necessary to saturate this extravenous blood would appear in the oxygen analyses as excess oxygen removed from the first 9-liter period. That this circulatory acceleration may have had a greater effect in removing oxygen from the alveoli than the hyperventilation had in providing it, is suggested by the fact that the oxygen content of the expired air was always lower during the beginning of the period of voluntary acceleration than later (see Table 1), whereas with uncomplicated hyperventilation it is usually increased immediately (Soley and Shock¹⁴).

In order to assess the quantity of oxygen which might be taken up in this way it would be necessary to have a quantitative measurement of the amount of excess ventilation, but a rough attempt

may nevertheless be interesting. Such an attempt, based on the data available, would involve certain assumptions. Fortunately it seems possible to approach the problem in two different ways, the necessary assumptions for which are entirely different. In the case of "A.L." (4/11/38) we see (Table 1) that an immediate effect of the command to accelerate is a fall in the oxygen content of the expired air in spite of the hyperventilation already discussed. Since the highest oxygen content of expired air is usually at the beginning of hyperventilation, we may be justified in assuming that such might have been the case here. On the basis of the two subsequent figures, let us assume that the maximum oxygen content attained by the subject can be attributed entirely to hyperventilation. The difference between this maximum value (17.63) and the value observed (16.48) during the first period might well have been due to the passage of oxygen into the newly released venous blood during this time. This difference (1.15) multiplied by the volume of air expired during the period (8.3 liters*) gives a value of 95 cc. for the amount of oxygen which might have been expected in the expired air but was not found. To regard this as stored in the newly released blood involves the further assumption that the metabolic rate does not vary greatly during the period of cardiac acceleration—an assumption which seems reasonable in view of the way in which the levels of increased pulmonary and circulatory activity are maintained.

TABLE 3.—CALCULATION OF "OXYGEN STORAGE."

	Experiment.			
	I.	II.	III.	IV.
Subject	A. L.	A. L.	A. B.	A. B.
Date of experiment	4/11/38	5/2/38	4/4/38	4/18/38
<i>Method I:</i>				
Observed % O ₂ in expired air attributed to hyperventilation	17.63	17.21	17.63	17.49
Observed % O ₂ in expired air of Period I	16.48	16.50	16.17	16.87
Difference	1.15	0.71	1.46	0.62
Cc. O ₂ "stored"	95	59	121	52
<i>Method II:</i>				
Volume of air in lungs (assumed)	3000	3000	3000	3000
Change in % O ₂ in expired air (basal—Period I)	0.43	0.41	-0.60	-0.68
O ₂ disappearing from lungs due to change in gas composition (cc.)	13	12	-18	-20
Measured excess O ₂ uptake during Period I (cc./min.)	142	139	143	131
Total O ₂ taken up in Period I (cc.)	155	151	125	111
Total excess metabolism (cc.)	240	320	330	95
Excess metabolism for Period I	79	104	99	29
O ₂ "stored" (cc.)	76	47	126	82

The other method of attacking this problem involves the assumption that the amount of air in the lungs is not greater than 3 liters

* This figure, 8.3, is the volume of the "9-liter" spirometer (9.19 liters) corrected for pressure, temperature, and water vapor.

and that its mean oxygen content does not change any more than that of the expired air. These limiting assumptions, as will be seen, give us a figure which is of the same order of magnitude as that already obtained. Thus in the same experiment, the quantity of oxygen absent from the lungs during the first 9-liter period of acceleration is not greater than $3000 \times .0043 = 13$ cc. oxygen. The increased oxygen intake in this period as compared with the resting period amounts to 142 cc. Adding this to the 13 cc. which have left the lungs, as shown by the changed oxygen content of the expired air, we have 155 cc. of oxygen to account for the excess metabolism during this period as well as the saturation of the newly liberated blood. From Table 2 we find that the total excess metabolism of the acceleration period was 240 cc. If we assume that the metabolic increase, like the circulatory displacements, was evenly distributed over the experimental period, we may divide it between the three acceleration collections in proportion to their duration. It then appears that 79 cc. excess oxygen were used during the period which is under consideration. After these 79 cc. have been subtracted from the 155 cc. above, there remain 76 cc. for the saturation of the stored blood. Considering the two calculations just made we may say that an amount of about 75 to 100 cc. of oxygen has left the lungs in excess of that which appears to have been required for metabolic needs. Table 3 shows the results of similar calculation on all 4 of the experiments.

It is not beyond the bounds of possibility that in "A.B." the increase of systolic without much change in diastolic pressure might have been achieved by a moderate vascular relaxation (of the epinephrine type, perhaps, since this subject reacted more slowly) which in turn would have increased the cardiac output and frequency without calling on the blood stores to any great extent. This suggestion is further supported by the somewhat less sudden appearance and disappearance of the phenomena in his case.

If the excess oxygen found in these calculations is taken up, as has been suggested by blood newly liberated from blood stores, it would be sufficient to saturate between $\frac{1}{2}$ and 2 liters of pulmonary artery blood. The former of these figures is based upon one of the higher figures for pulmonary arteriovenous oxygen difference (130 cc. per liter) observed by Grollman; the latter and larger figure upon an arteriovenous oxygen difference of 50 cc. per liter. The blood released from the stores, however, would almost certainly differ from pulmonary artery blood in being more venous and having a higher oxygen capacity since at least some of it would come from the spleen. This makes it possible that the oxygen in question might be absorbed by considerably less than a liter of mobilized blood. Barcroft¹ regards his estimate of a 1-liter blood mobilization for man as conservative.

The above considerations with respect to oxygen uptake are

borne out by the indications of the carbon dioxide analyses (Table 1) which indicate excess carbon dioxide elimination, but it does not seem possible to deal with this gas on a similar basis because of the vast stores of it throughout the body and of the ease with which it may be liberated in response to the production of fixed acids.

It might be suggested, on the other hand, that the sudden uptake of oxygen and evolution of carbon dioxide might be more simply explained by a sudden burst of metabolism. The gas analysis figures offer no absolute refutation of this contention, but it is difficult to visualize a sudden violent metabolic activity of about 1 minute's duration without any corresponding disturbance appearing in the cardiovascular and pulmonary system.

Discussion. The incidence of the ability voluntarily to accelerate the heart has been much discussed in the 9 reports cited, but there does not appear to have been any attempt to investigate its frequency in adequately large groups. The extreme view is that of Van de Velde,¹⁸ based on a series of 5 cases, of which 4 showed the phenomenon, which holds that the power is almost universal and that acceleration can be induced by anyone after a little practice.

The pharmacology of the phenomenon has been studied, particularly with reference to atropine, in attempts to throw light on the efferent nervous or chemical mechanisms involved, but the uncertainty as to the adequacy of any given dosage has made for confusion in the findings. Tarchanoff observed that the power was in abeyance under the influence of subanesthetic doses of nitrous oxide. Oddly enough, it was while submitting to this drug that one of our subjects (A. B.) first noticed his ability to alter his pulse rate.

Dilatation of the pupil, increased blood pressure,¹⁶ perspiration, increased oxygen consumption,³ and hyperventilation¹⁶ have all been noted as phenomena concomitant with voluntary acceleration of the pulse, but it is not recorded that acceleration has ever been produced without the accompaniment of them.

Summary. Two subjects are discussed; both of them are able voluntarily to accelerate their pulse rates at the word of command. This acceleration is accompanied by increased systolic and diastolic blood pressures, increased rate of respiration, ventilation volume, oxygen uptake and carbon dioxide output. The onset and disappearance are abrupt.

The quantitative consideration of the magnitude and time relations of these functions indicates that there is a true hyperventilation with excess elimination of carbon dioxide, a true increase in metabolism with excess oxygen utilization, and a hypercirculation, or circulation in excess of the metabolic requirement. Epinephrine might be responsible for the cardiac acceleration and the increased blood pressure and, by discharge of blood reservoirs, for the increased circulation. But it is believed that the phenomenon appears and disappears so rapidly that epinephrine cannot be solely held to

account. In the 9 reports cited, covering some 15 other cases of voluntary acceleration of the heart, there is no instance in which the acceleration was not accompanied by one or more of the other phenomena described.

Grateful acknowledgment is hereby made to Mrs. Kathryn Long and Mr. Theodore Chernikoff for technical assistance, to the W.P.A. (O.P. No. 665-08-3-30, Unit A-8) for clerical and statistical work, and to the Board of Research of the University of California for financial support.

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BRUCELLOSIS WITH ENDOCARDITIS.

REPORT OF A CASE WITH FAILURE OF SULPHANILAMIDE THERAPY.

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Few cases of proved endocarditis occurring during the course of undulant fever (brucellosis) have been reported. Hughes,⁷ in 1897, reported the postmortem findings in 3 fatal cases of Malta fever; in 1, vegetations were discovered on thickened mitral valve leaflets and the organisms were obtained from the spleen; the second was a return case with a fatal relapse with positive splenic cultures, a small aneurysmal dilatation above the posterior left semilunar valve, and vegetations on all 3 cusps; the third had warty vegetations on the mitral valves, and culture showed the "characteristic growth from the spleen." Scott and Saphir¹⁸ observed a patient

with rheumatic heart disease who developed undulant fever complicated by embolic accidents. Repeated blood cultures were positive for *Brucella abortus*. Postmortem examination showed numerous friable vegetations superimposed on scarred mitral and aortic valve leaflets. Rennie and Young¹⁶ observed a patient with positive blood culture for *Brucella abortus*, whose illness was also complicated by embolic phenomena. Postmortem examination showed friable vegetations containing numerous aggregations of bacilli resting on a stenotic and calcareous mitral valve. de La Chapelle⁵ observed a patient with positive blood culture for *Brucella melitensis* A. Postmortem examination revealed that the anterior aortic valves were almost completely destroyed and replaced by a mass of fused vegetations blocking the aortic orifice. The posterior aortic valve was thickened and supported a pea-sized vegetation. Levy and Singerman¹³ reported a fatal case with positive blood culture for *Brucella melitensis* in which the mitral valve showed a friable vegetation, the valve itself showing fibrous thickening. A smear from the vegetation showed many small Gram-negative bacilli. Gounelle and Warter⁹ observed a patient with positive blood culture for *Brucella melitensis*. Postmortem findings included ulcerovegetative endocarditis of a calcific aortic ring. Casanova and d'Ignazio⁴ reported a case of aortic endocarditis developing after 3 months of Malta fever. Postmortem findings included vegetative aortic endocarditis and infarcts in the spleen and kidneys from which *Brucella melitensis* was obtained in pure culture. Three additional cases of endocarditis occurring during the course of undulant fever, but without postmortem confirmation, have been reported by Lagriffoul, Roger, and Sarradon,¹² Gate and Ravault,⁸ and Knighton.¹¹ Despite the increased incidence of recognized brucella infection there is still a scarcity of reported cases of brucellosis with endocarditis. It is for this reason that we present the following case of endocarditis occurring during the course of brucellosis, with a fatal termination despite treatment with sulphanilamide.

Case Report. B. C., a 47-year-old farmer, was admitted to the University Hospital on June 6, 1938. Multiple joint pains occurred at the age of 12. In early adult life he had been refused insurance because of "heart disease." Progressive shortness of breath had been present for 4 years. The patient drank raw milk but had never had abortions among his cattle, which, however, had not been tested for Bang's disease. In February, 1938, the patient had had a severe sore throat with temperature elevation to 103°. He remained acutely ill for 10 days and then recovered except for the daily return of afternoon fever ranging from 100° to 102°, on one occasion to 105°, with drenching night sweats. Despite bed rest he noted increasing weakness and fatigue, shortness of breath, a 10-pound weight loss, and migratory joint pain. The family physician began a course of sulphanilamide, which was continued for 2 weeks, at first 6 gm., then 5 gm., and later 4 gm. daily. The joint pain disappeared 3 days after beginning sulphanilamide therapy.

On admission to the University Hospital the patient's temperature was

101.8°, pulse 116, respirations 20, and blood pressure 120/74. The skin was warm and moist. The pupils were slightly irregular and reacted sluggishly to light and accommodation. There was no lymphadenopathy. The chest was negative. The left border of cardiac dullness was 10 cm. to the left of the midsternal line in the fifth interspace. The cardiac rate was rapid but the rhythm was regular. There was a systolic murmur at the apex transmitted into the axilla and heard over the entire chest. The peripheral vessels were moderately tortuous and sclerotic. The abdomen was negative. The prostate was not enlarged. Examination of the extremities revealed no abnormalities.

The Kahn test was negative. Admission urine examination was negative, and subsequent weekly examinations showed no urinary abnormality. Hemoglobin was 84%, erythrocyte count 4,340,000, and leukocyte count 8800, with a differential of 66% neutrophils, 4% eosinophils, 25% lymphocytes, and 5% monocytes. The routine stool examinations were negative. The patient's weight on admission was 142.5 pounds; during the 57 days of hospitalization his weight gradually decreased to 127 pounds. The temperature varied from 97.6° to 105°, showing an afternoon peak which was more septic than undulant in character; the average for the afternoon peak was 103°. The pulse varied over a wide range from 70 to 150 per minute with close correlation with the fluctuations of temperature.

On June 9, 1938, an endermal test of 0.1 cc. Brucellergin showed a positive reaction, the blood serum showed positive agglutination for *Brucella abortus* in dilutions up to and including 1 to 1280, and the neutrophils showed 8% slight, 58% moderate, and 34% marked cytophagocytic activity to *Brucella abortus* organisms. A blood culture taken at that time was subsequently reported as showing *Brucella abortus* organisms.

On June 10, 1938, the patient received 25 million killed typhoid organisms in the morning and again in the afternoon, the temperature rising to 105° 90 minutes after each injection. On June 16, the patient received 2 doses of 100 million killed typhoid organisms each, the temperature again rising to 105° 90 minutes after each injection. No appreciable therapeutic result was noted. On the 16th, sound tracing (Fig. 1) taken at the cardiac apex showed splitting of both heart sounds and a systolic murmur. On the 20th, sulphanilamide therapy was instituted; by the 23d, a blood sulphanilamide level of 9 mg. per 100 cc. was reached, and a blood culture obtained on that day was subsequently reported as showing no growth. Four days later, the blood sulphanilamide level was 6.6 mg. and on June 29, sulphanilamide therapy was discontinued on its ninth day because of cyanosis, anorexia, and what was at that time regarded as a favorable effect on the febrile course. However, shortly thereafter the temperature curve again became septic, though blood culture obtained on July 6 was subsequently reported as showing no growth. One week later, scattered petechiæ appeared over the right lower leg. A blood culture obtained on that day was subsequently reported as showing *Brucella abortus*, the neutrophils showed 32% moderate and 68% marked cytophagocytic activity to *Brucella abortus* organisms, and the blood serum showed positive agglutination for *Brucella abortus* up to and including 1:1280, with cross-agglutination for *Brucella suis*, 1:640, and *Brucella melitensis*, 1:40. At that time, a clinical diagnosis of *Brucella abortus* endocarditis was made and sulphanilamide therapy resumed. Also, on that day roentgenographic examination of the chest showed no evidence of active intrathoracic disease, but a slight increase in the heart size as compared with the previous examination on admission (Fig. 3). On July 16, an aortic diastolic murmur was heard for the first time. On that day many more petechiæ were present. Two days later, the patient received a 700 cc. blood transfusion. On the 23d, the blood sulphanilamide level was 11.2 mg. and the petechiæ on the ankle had



FIG. 1.—Sound tracing taken at the cardiac apex on admission, showing splitting of both heart sounds and a systolic murmur.

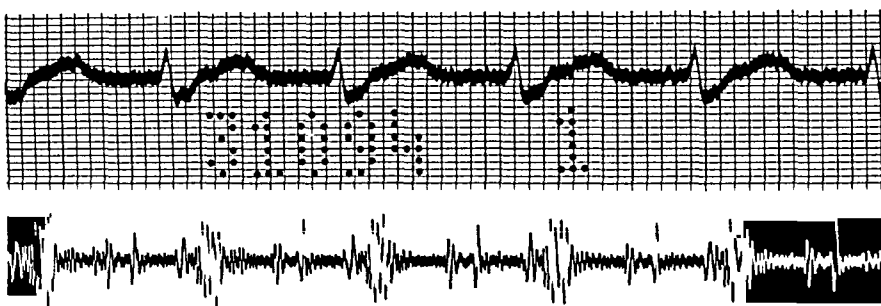


FIG. 2.—Sound tracing taken at the cardiac apex 6 weeks after admission, showing the long split first sound and systolic murmur as before, and the new presystolic and protodiastolic sound and the prominent new protodiastolic gallop sounds. The accompanying electrocardiogram shows right bundle branch block, and evidence of progressive myocardial damage.

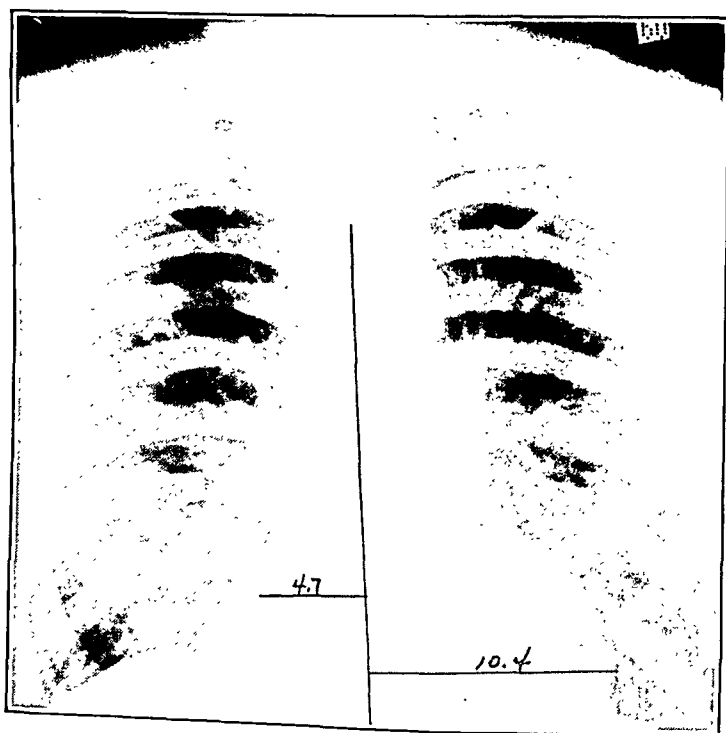


FIG. 3.—Roentgenographic appearance of the chest on admission, showing no evidence of intrathoracic disease, and relatively normal cardiac silhouette.

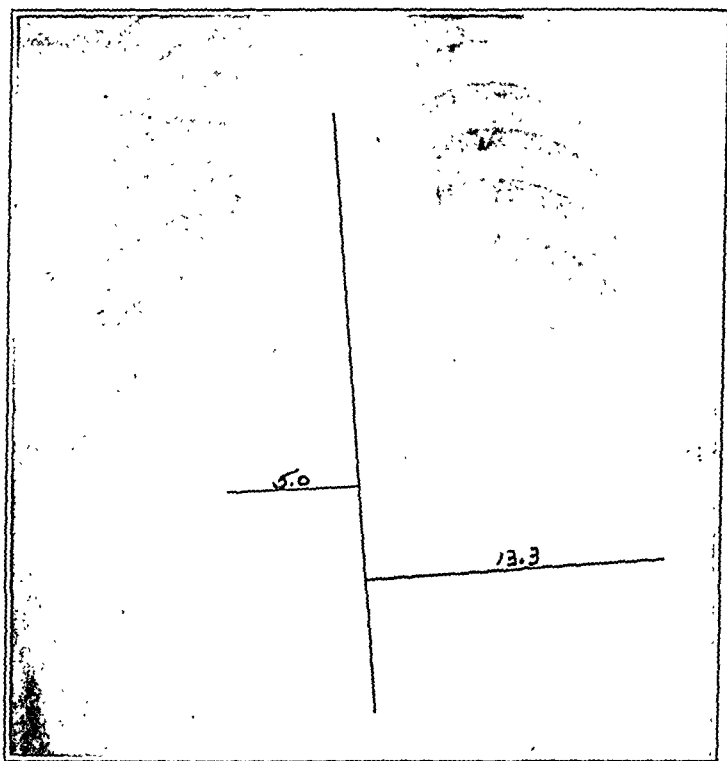


FIG. 4.—Roentgenographic appearance of the chest 7 weeks after admission, showing the marked increase in the size of the cardiac silhouette, and accompanying pulmonary congestion at both lung bases.



FIG. 5



FIG. 6

FIG. 5.—Aortic valve showing the large ulcero-thrombotic vegetation almost occluding the lumen of the aortic valve, and resting on scarred valve leaflets.

FIG. 6.—Right auricle, showing an aneurysmal dilatation of the septal wall with its mouth (not visible) in the area of ulceration of the aortic valve.

cleared. A sound tracing (Fig. 2) taken at the cardiac apex showed a long split first sound, a systolic murmur, both presystolic and protodiastolic extra sounds, and a prominent protodiastolic gallop sound; the accompanying electrocardiograms showed right bundle branch block. On July 24, the patient complained of sudden transient precordial pain, respirations increased, and a faint precordial friction rub was heard. On the following day the leukocyte count had risen to 19,000, the cardiac apex was percussed at 11.5 cm. to the left of the midsternal line at the fifth interspace, and there was a distinct friction rub at the apex. Sulphanilamide therapy was discontinued (on twelfth day). On August 1, roentgenographic examination of the chest (Fig. 4) showed a marked increase in the size of the cardiac shadow since admission, and signs of diffuse pulmonary congestion. An electrocardiogram showed right bundle branch block and changes suggestive of extensive myocardial damage. That evening respirations ceased.

Necropsy Findings. Although a complete necropsy was done, only the pertinent findings are reported. The thorax contained 650 cc. of watery yellow fluid on the left and 500 cc. on the right. The pericardium was slightly distended and contained 200 cc. of clear yellow fluid; the pericardial surfaces were smooth.

The heart was roughly globular in shape, measured 18.5 by 13.5 by 6.25 cm. and weighed 500 gm. The mitral valve was 100 mm. in circumference, the valve flaps showed normal apposition with no fibrosis. The aortic valve measured 54 mm. in circumference and on the posterior valve flap on the left, and also involving to a lesser extent the posterior valve flap on the right, was a large firm ulcerative thrombotic vegetation measuring 1.5 by 3 cm. in size, almost completely occluding the lumen of the aortic valve (Fig. 5). There were patchy areas of calcification throughout the aortic valve leaflets, and at the attachment of the vegetation to the myocardium was an area of calcification. In the right auricle was a mass extending out into the lumen of the auricle for a distance of 3 cm., measuring 1.5 by 1.5 cm. in diameter. This mass (Fig. 6) had ulcerative surfaces and appeared to be an aneurysmal dilatation of the septal wall with its mouth in the area of ulceration of the aortic valve. The tricuspid valve showed old adhesions between the two valve flaps with secondary contraction and limitation of free movement. On the posterior medial flap was a 1 cm. sized ulcerative vegetation showing superficial thrombosis. Microscopic examination showed old sclerosis and calcification of the aortic valve with acute vegetative endocarditis made up of colonies of organisms, fibrin, and large cells resembling Aschoff cells. There was advanced coronary atherosclerosis and calcification in the stroma.

The spleen was large, soft and flabby. It weighed 380 gm. and showed congestive changes. The liver weighed 2150 gm. and showed an acute exacerbation of chronic congestion (nutmeg liver).

Bacteriologic Studies.* The organism grown from the blood cultures obtained from the patient was a tiny Gram-negative cocco-bacillus which would not grow without carbon dioxide. It did not ferment any of the carbohydrates tested. It agglutinated specific antisera (Mulford's) as follows:

	Br. abortus.	Br. melitensis.
1st blood culture	1:2560	1:320
2d blood culture	1:640	1:320
3d blood culture	1:2560	1:640

The dye and hydrogen sulphide production reactions were puzzling so the culture obtained from the patient's blood was then sent to Dr. I. Forest

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Huddleson, Michigan State College, who stated that "we have found the culture to be *Brucella abortus*. The fact that it will not grow in the absence of 10% carbon dioxide air content immediately identifies it as an *abortus*. We were unable to grow your culture on our thionin dye plates, but we were able to on the basic fuchsin, using Difco Tryptose agar media. The organism did not produce its typical hydrogen sulphide reaction."

Comment. We have presented a case of brucellosis who developed an acute ulcerovegetative endocarditis on previously existing aortic valvular scars. In addition to typhoid vaccine induced hyperpyrexia, the patient received 3 courses of sulphanilamide therapy. Sulphanilamide and related compounds have been reported by numerous authors^{1-3,6,10,14,15,17,19-22} to be almost uniformly adequate for uncomplicated brucellosis but it was of no value in this case.

The patient gave a history of rheumatic fever. The organisms of a *Brucella abortus* septicemia probably lodged and vegetated upon the valves scarred by the old valvulitis. This mechanism of endocarditis production is similar to that observed in cases of subacute bacterial endocarditis. The valvular vegetations undoubtedly served as a focus to reinfect the blood stream following each course of sulphanilamide, as was evidenced by a negative blood culture obtained after one such course, and the reappearance of a *Brucella abortus* septicemia heralded by petechiæ. The presence of preëxisting cardiac valvular scars, which may serve as a foundation for the formation of a vegetative focus of reinfection, may be responsible for occasional failures in the use of sulphanilamide as a chemotherapeutic agent in the treatment of brucellosis.

Summary. 1. Nine previously reported cases of brucellosis endocarditis with postmortem confirmation have been reviewed.

2. Another autopsied case of brucellosis with aortic vegetative endocarditis, refractory to 3 courses of sulphanilamide therapy, has been presented.

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THE EFFECT OF SULPHANILAMIDE UPON SPERMATOGENESIS IN MAN.

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THE administration of sulphanilamide derivatives to man has been thought to influence spermatogenesis.^{1,2} To study this observation, the semen from 11 selected patients was analyzed before and after sulphanilamide was given.

Method of Examination. The semen was obtained by having the patient ejaculate directly into a wide mouth, dry, glass container, and the amount of the specimen was measured in cubic centimeters, after liquefaction had occurred. The spermatozoa were then counted on a standard blood counting chamber. A white blood counting pipette was used, and a diluent of soda, formalin and water. Thirty-two to sixty-four white blood counting squares, depending upon the concentration of the spermatozoa, were counted and the ordinary calculation used to express the number of spermatozoa in a cubic centimeter. The total number of spermatozoa in the specimen was obtained by multiplying the number in each centimeter by the cubic centimeters in the specimen.

The table shows the number of specimens examined; the total number of spermatozoa and the percentage alive, before, during, and after treatment; and the time specimens were obtained in relationship to the treatment.

The sulphanilamide was given by mouth in the form of prontylin up to a total of 40 grains daily, except when the drug was not tolerated, and then the dose was reduced, or the patient put on a rest period for 2 or 3 days. The duration of treatment, in days, is given in the table.

Conclusions. In contrast to other reports, these data indicate that in 11 patients there were no noteworthy effects upon the total number, nor percentage of live spermatozoa from the use of sulphanilamide.

Such variations as shown in the total spermatozoa counts during and after treatment are no greater than the variations which occurred before the drug was given.

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TABLE 1.—EFFECT OF SULPHANILAMIDE ON SPERMATOZOA.

Patient.	Age.	Before treatment.		Treatment.		During and after treatment.			
		Total spermatozoa count (millions).	% live sperm.	Amt. of sulph-anil-amide given (gr.).*	No. of days given.	Total spermatozoa count (millions).	% live sperm.	Time specimen was obtained.	
								After treatment begun (days.)	After treatment stopped (days.)
L. Z.	23	306.1	20	600	24	30.7	10	3	
		149.4	10	55.9	15	13	
		151.8	0	183.6	90	..	4
						184.7	85	..	25
						463.4	90	..	32
						338.5	85	..	36
W. S.	18	859.3	90	800	56	768.0	90	7	
		797.9	0	481.2	75	20	
		352.0	90	459.3	90	28	
		930.0	90	473.8	70	44	
						334.2	90	51	
						531.2	75	54	
						300.0	80	..	4
F. K.	59	209.0	75	400	18	414.4	75	10	
		264.0	80	583.2	90	4	
		118.4	85						
		260.4	75						
		247.2	60						
		166.3	20						
		209.7	75						
J. W.	59	207.9	90	800	42	308.6	80	4	
		257.3	90	554.2	75	11	
		278.1	85	301.8	60	29	
						341.9	70	..	23
						390.6	35	..	37
J. H.	48	320.9	45	600	22	274.4	40	4	
		278.8	15	345.6	40	10	
		172.8	60						
		142.0	85						
D. McA.	45	277.8	80	400	24	294.4	90	4	
		294.0	80	255.8	85	8	
		453.6	95	256.8	80	18	
		278.4	85						
		476.8	80						
		139.9	70						
E. C.	32	172.2	80	400	16	145.8	75	4	
		143.7	80	175.0	85	10	
		127.7	90	123.9	65	..	8
		136.4	90	129.3	80	..	22
G. G.	48	1,042.4	90	800	58	800.0	70	7	
		543.2	80	136.2	60	14	
		363.3	90	638.0	85	21	
		489.6	85	624.0	75	28	
						498.4	50	35	
						145.8	70	56	
						345.0	80	..	12
R. M.	18	163.2	85	600	20	252.7	85	7	
		234.3	85	240.4	85	14	
		207.0	90	238.3	80	18	
		235.4	80	276.1	90	..	2
						261.3	85	..	6
E. R.	22	471.4	90	800	57	579.9	90	7	
		395.5	90	369.0	80	12	
		391.7	70	424.6	80	21	
						384.8	85	28	
						422.1	85	32	
						400.2	90	43	
						444.8	90	51	
						485.8	90	57	
						460.6	85	..	14
P. K.	28	348.7	75	720	36	327.1	75	11	
		296.0	25	304.4	50	18	
		346.8	80	303.3	60	25	
		401.9	65	331.5	85	28	
						290.6	60	36	

* The sulphanilamide was given by mouth under name of "Prontylin."
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TREATMENT OF PNEUMONIA WITH TYPE-SPECIFIC IMMUNE RABBIT SERUM.*†

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TYPE-SPECIFIC immune rabbit serum was first proposed for the treatment of pneumococcus pneumonia by Horsfall, Goodner, MacLeod, and Harris⁴ in May, 1937. Its introduction for clinical use followed in logical sequence upon their previous experimental studies. Therein it had developed that this product differs from horse antiserum in a number of ways, several of which suggest that rabbit antiserum might prove to be the more efficient.^{3a} It had been found that the rabbit produces serum of considerably higher mouse-protective potency than the horse; that the rabbit antibody is relatively much smaller in size than the horse antibody and therefore might be expected to penetrate tissues more readily;² that the mouse-protective power of rabbit antiserum is maintained regardless of the size of the dose,^{1a} although that of horse antiserum fails entirely when greater than optimal amounts are given; and that the mouse-protective power of rabbit antiserum is not inhibited by the addition of physiologic amounts of cholesterol and cephalin, as is the case with horse antiserum.^{1b}

In February, 1938, these investigators^{3b} reported their experience with a series of 67 patients treated with unconcentrated type-specific antipneumococcus rabbit serum prepared according to a definite technique. Included in the series were cases of Types I, II, III, V, VI, VII, VIII, XIV, and XVIII. Of 13 patients with Type III pneumonia, 6 died, and the authors concluded there was no evidence that homologous rabbit antiserum had been of benefit in this type. However, of the remaining 54 patients, only 1 with Type I and 1 with Type II pneumonia died. The resulting mortality rate was 4% for 25 Type I cases, 10% for 10 Type II cases, and 3.7% for the whole series exclusive of cases of Type III.

In August, 1938, Loughlin, Bennett, and Spitz⁵ reported a series of 69 patients with lobar pneumonia similarly treated. These included cases of Types I, II, V, VII, VIII, and XIV. Of 28 patients with Type I pneumonia, 3 died—a mortality of 10.7%. Of 16 patients with Type II pneumonia, 2 died—a mortality of 12.5%. As these were the only fatalities, the mortality rate for the whole series was 7.2%.

* Read before the monthly scientific meeting of the Allegheny County Medical Society, December 20, 1938.

† Valuable aid in this study was given by Dr. Frank A. Pugliese.

In this paper a report is made of an additional series of 45 patients treated with type-specific antipneumococcus rabbit serum during the past year in Pittsburgh. Included in the series are cases of pneumonia of Types I, II, IV, V, VII, and VIII. The only factor entering into their selection was the availability of a homologous immune serum at the time of their admission. In the majority of cases the product employed was unconcentrated, and similar to that used by the aforementioned investigators. In a few of the more recent cases a concentrated preparation was administered.

All cases reported had roentgenographic evidence of consolidation, and either a positive blood culture or sputum in which the pneumococcus was the predominating organism. A history, physical examination, urine analysis, blood count, blood culture, sputum examination, and roentgenogram of the chest were obtained routinely on admission. Blood cultures were taken at 2-day intervals or more frequently when indicated. Identification of the type of pneumococcus present in the sputum was made by the Neufeld method and in many cases confirmed by passage through the mouse. Prior to instituting treatment all patients were given ophthalmic and intracutaneous tests for sensitivity to the specific serum which was to be used. The usual precautions, advisable in all serotherapy, were observed. Where a positive intracutaneous test was associated with a negative ophthalmic test, the administration of serum was undertaken, but with more than the usual caution.

All serum was given intravenously. At first, doses of 20,000 units were given at 2-hour intervals until the temperature fell and showed no further tendency to become elevated. Later this plan of treatment was altered, as the administration of larger doses seemed preferable in order to introduce the total dose in as short a time as possible and spare the patient the discomfort of unnecessarily numerous injections. Thereafter, following an initial dose of 20,000 units, one or more doses of 100,000 units were given until it was apparent that the disease was being brought under control. Subsequently, smaller doses were given as seemed indicated until recovery was complete. In several patients one injection of 100,000 units following the initial dose of 20,000 units was sufficient to secure the desired result. Supplementary treatment consisted only of dietary regulation and symptomatic treatment, including oxygen administration, when indicated.

Ten patients with Type I pneumonia were treated. The important features of these cases are outlined in Table 1. They ranged in age from 21 to 55 years. Three patients had consolidation of more than one lobe. Serum treatment was instituted on the second day of the disease in 2 patients, the third day in 3 patients, the fourth day in 3 patients, and the fifth day in 2 patients. The quantity of serum administered varied from 120,000 to 300,000 units, and averaged 207,000 units. However, the first 3 patients in this group were

given additional serum after the fever had subsided, because it was feared that a reversal of the favorable trend might occur if treatment were stopped too soon. Disregarding this additional dosage, the average quantity of serum administered prior to recovery was 185,000 units. In 9 patients the course of the disease terminated prematurely, recovery from the acute phase having occurred in from 9 to 32, or an average of 17 hours after serum administration was started. Two patients were delirious on admission. Pneumonia in 1 patient was complicated by post-tuberculous fibrosis of the lung. Only 1 of this group had bacteremia. All patients with Type I pneumonia recovered.

TABLE 1.—DATA ON CASES OF TYPE I PNEUMONIA TREATED WITH TYPE I RABBIT ANTISERUM.

Name.	Age.	Sex.	Lobes consolidated.	Bacteremia, colonies per cc.	Day of disease serum started.	Day of disease recovered or died.	Serum dosage in thousand units.	No. of doses given.	Recovery, hours after serum.	Serum reactions.		Result.
										Chill.	Serum sickness.	
L. H.	21	F	1	..	4	4	140	7	10	1	..	R
G. H.	28	M	1	..	4	4	240	12	18	R
A. J.	40	F	1	..	4	4	200	10	16	..	+	R
M. T.	55	F	2	..	3	4	120	2	9	2	+	R
A. N.	38	M	1	..	5	6	240	3	12	..	+	R
J. M.	26	M	1	..	3	4	300	3	23	..	+	R
W. A.	21	M	1	..	2	3	240	6	21	..	+	R
M. A.	53	M	2	..	3	4	160	2	32	R
W. R.	33	M	2	..	5	8	280	3	50	..	+	R
F. M.	26	F	1	<1	2	3	150	2	12	..	+	R

Twenty patients with Type II pneumonia were treated. The important features of these cases are outlined in Table 2. Their ages ranged from 13 to 58 years. Three patients had consolidation of more than one lobe. Serum treatment was instituted on the first day of the disease in 1 patient, the second day in 8 patients, the third day in 4 patients, the fourth day in 5 patients, the sixth day in 1 patient, and the seventh day in 1 patient. The quantity of serum administered to those patients who recovered varied from 100,000 to 600,000 units, and averaged 299,000 units. However, disregarding additional serum given to 4 patients in this group after the fever had subsided, the average quantity administered was 277,000 units. In 16 patients the course of the disease terminated prematurely, recovery from the acute phase having occurred in from 10 to 60, or an average of 27 hours after serum administration was started. In 1 of the remaining patients serum treatment was instituted on the seventh day because of intense toxemia, and crisis occurred within 12 hours. Of the 20 patients with Type II pneu-

monia 19 recovered; 1 of these had syphilis, 2 were delirious on admission, and 1 had chronic cardiac valvular disease with auricular fibrillation and a blood culture showing innumerable colonies per cc. Four patients in this group had bacteremia. The one death occurred in a patient whose blood culture showed 50 colonies per cc. and who developed pneumococcus meningitis.

TABLE 2.—DATA ON CASES OF TYPE II PNEUMONIA TREATED WITH TYPE II RABBIT ANTISERUM.

Name.	Age.	Sex.	Lobes consolidated.	Bacteremia, colonies per cc.	Day of disease serum started.	Day of disease recovered or died.	Serum dosage in thousand units.	No. of doses given.	Recovery, hours after serum.	Serum reactions.		Result.
										Chill.	Serum sickness.	
C. C.	25	F	1	..	3	4	220	11	15	R
G. G.	24	M	1	..	3	4	240	12	24	R
H. J.	42	M	1	..	2	3	420	12	33	R
V. T.	53	M	1	..	2	4	320	16	45	R
D. H.	37	M	1	..	2	5	320	16	60	..	+	R
R. T.	38	M	1	..	3	4	180	9	44	..	+	R
M. V.	34	F	1	<1	2	3	140	7	15	..	+	R
C. M.	55	F	1	..	1	3	400	17	33	..	+	R
H. S.	48	M	1	..	3	6	560	15	78	1	..	R
S. K.	15	M	1	..	4	6	320	8	41	..	+	R
J. F.	42	M	1	..	2	3	600	14	36	R
P. H.	16	F	1	..	4	5	120	2	10	1	+	R
D. J.	13	F	1	..	4	5	120	2	10	1	+	R
D. J.	58	M	3	50	6	14	800	11	D
H. S.	49	M	1	10	2	4	300	3	26	1	+	R
W. N.	15	M	2	..	7	7	240	3	12	R
J. Z.	53	F	1	*	2	2	360	9	23	..	+	R
J. M.	30	M	2	..	4	5	460	7	22	1	+	R
R. A.	54	M	1	..	4	5	270	4	27	2	..	R
F. S.	32	F	1	..	2	3	100	3	15	R

* Innumerable.

The important features of cases of pneumonia of Types IV, V, VII, and VIII are shown in Table 3. Only 1 patient with Type IV pneumonia was treated—a 46-year-old male with consolidation of two lobes. He had a bacteremia of 60 colonies per cc., and was also afflicted with cerebrospinal syphilis. Serum treatment in 200,000 unit dosage was started on the fourth day of his illness. He recovered by crisis within 8 hours, when only 160,000 units of the total dosage had been administered.

Seven patients with Type V pneumonia were treated. Their ages ranged from 21 to 57 years. Four patients had consolidation of more than one lobe. Serum treatment was instituted on the second day of the disease in 1 patient, the third day in 3 patients, the fifth day in 2 patients, and the seventh day in 1 patient. The quantity of serum administered varied from 200,000 to 400,000 units, and

averaged 280,000 units. In 5 patients the course of the disease terminated prematurely, recovery from the acute phase having occurred in from 8 to 32, or an average of 16 hours after serum administration was started. In 1 other patient, serum treatment was not started till the seventh day of the disease, when the blood culture first became positive. This patient recovered by crisis within 15 hours. One patient was delirious on admission, 1 had syphilis, and another, whose fever did not subside until 10 days after the onset of pneumonia, suffered from a concurrent attack of pyelitis. Two members of this group had bacteremia. One of these, with a blood culture of 40 colonies per cc., had marked pulmonary edema on admission and apparently had a hopeless prognosis. All 7 patients recovered.

TABLE 3.—DATA ON CASES OF PNEUMONIA OF TYPES IV, V, VII, AND VIII TREATED WITH HOMOLOGOUS RABBIT ANTISERUM.

	Name.	Age.	Sex.	Lobes consolidated.	Bacteremia, colonies per cc.	Day of disease serum started.	Day of disease recovered or died.	Serum dosage in thousand units.	No. of doses given.	Recovery, hours after serum.	Serum reactions.		Result.
											Chill.	Serum sickness.	
Type IV	E. P.	46	M	2	60	4	4	200	4	8	R
Type V	P. M.	57	M	3	..	5	10	240	12	120	R
	G. J.	35	M	2	<1	7	8	300	3	15	R
	C. S.	45	M	1	..	3	3	200	3	8	..	+	R
	T. C.	37	M	2	..	3	4	320	3	32	2	..	R
	C. S.	21	M	1	..	3	4	300	4	16	R
	J. C.	37	M	1	..	2	2	200	3	8	1	..	R
	J. T.	55	M	2	40	5	5	400	4	14	1	+	R
Type VII	S. G.	32	M	2	..	2	7	460	6	104	..	+	R
	G. S.	51	M	1	*	9	17	540	7	..	1	..	D
	F. D.	19	M	1	..	3	4	200	3	9	1	..	R
Type VIII	H. L.	34	M	1	..	3	3	400	7	9	..	+	R
	L. S.	29	M	1	..	4	5	220	3	12	1	+	R
	S. D.	32	M	1	..	2	3	160	3	13	R
	F. C.	38	M	1	20	4	5	220	3	16	R

* Innumerable.

Three patients with Type VII pneumonia were treated. One, 32 years old, with consolidation of two lobes and a negative blood culture, recovered by lysis on the seventh day of his illness, although serum treatment in 460,000 unit dosage had been instituted on the second day. Another patient, with consolidation of one lobe and a negative blood culture, recovered by crisis on the fourth day of his illness, 9 hours after serum administration in 200,000 unit dosage

had been instituted. The remaining patient, a 51-year-old male with consolidation of one lobe, had a bacteremia of innumerable colonies per cc. when admitted on the ninth day of his illness. Although 540,000 units of serum were administered, meningitis developed and death occurred 8 days later.

Four patients with Type VIII pneumonia were treated. Their ages ranged from 29 to 38 years. All had consolidation of only one lobe. Serum treatment was instituted on the second day of the disease in 1 patient, the third day in 1 patient, and the fourth day in 2 patients. The quantity of serum administered varied from 160,000 to 400,000, and averaged 250,000 units. However, disregarding 120,000 units additional serum given to 1 patient in this group after the fever had subsided, the average quantity administered was 220,000 units. In all 4 patients the course of the disease terminated prematurely, recovery from the acute phase having occurred in from 9 to 16, or an average of 13 hours after serum administration was started. One patient had diabetes mellitus and syphilis, and 2 were alcoholics and were delirious. One patient in this group had bacteremia.

Comment. In this series of 45 patients with pneumococcus pneumonia 2 deaths occurred—a mortality rate of 4.4%. Twelve patients had involvement of more than one lobe; in 6 of these the consolidation was bilateral. No cases of empyema were observed. In 1 case a sterile pleural effusion formed, but was absorbed without becoming infected.

In 36 (80% of the cases) the course of the disease was apparently shortened by serum administration, recovery from the acute phase, as evidenced by subsidence of fever, reduction of pulse and respiratory rates and a marked improvement in the subjective symptoms, having occurred in from 8 to 60, or an average of 20 hours after institution of specific therapy. In 2 of the remaining cases, treatment was not started till the seventh day of the disease; and in 1 other case the clinical course was modified by the presence of active pyelocystitis of non-pneumococcal origin.

In 15 patients, apparent recovery from the active pneumonic process was followed for several days by a low-grade irregular fever, which was unattended by other symptoms or signs of illness. In 11 of these the fever terminated with some frank manifestation of serum sickness, such as urticaria or polyarthrititis. In the other 4 it subsided without any other evidence of serum sickness having appeared.

Ten patients in this series of cases had bacteremia. Included among them were 1 case of Type I pneumonia, 4 cases of Type II, 1 of Type IV, 2 of Type V, 1 of Type VII, and 1 of Type VIII. Although the only 2 fatal cases encountered were members of this group, it is important to note that in 4 cases with bacteremias of from 20 to innumerable colonies per cc. recovery occurred within from 8 to 23 hours of the institution of serum treatment.

Certain features of the 2 fatal cases are of interest. One patient, a 58-year-old male with Type II pneumonia, was admitted on the sixth day of his illness with consolidation of the whole right lung. When first seen he had a bacteremia of 50 colonies per cc. Serum (240,000 units) was given over the sixth and seventh days of the disease. As at this time the temperature dropped to normal and the patient showed marked improvement, serum administration was stopped. After 2 days of approximately normal temperature, fever again developed, along with symptoms and signs of meningeal irritation. Notwithstanding the administration of 460,000 additional units of antiserum intravenously and 100,000 units intraspinally, the patient died of Type II pneumococcus meningitis on the fourteenth day of the disease. Five consecutive blood cultures had shown 50, 0, 10, 0, and 5 colonies per cc., respectively. In view of the patient's age, the late stage of the disease at the time the patient came under observation, and the heavy bacteremia, probably much more than 240,000 units of serum should have been administered without interruption, regardless of the apparent immediate improvement.

The other patient, a 51-year-old male with Type VII pneumonia, was admitted on the ninth day of his illness with consolidation of the left lower lobe. Before serum administration was started he had a bacteremia of innumerable colonies per cc. On the following day the blood culture showed 25 colonies per cc., and on the second day after admission less than 1 colony per cc. Simultaneously the patient showed considerable clinical improvement subjectively and objectively. However, after 540,000 units had been administered, the available supply of serum was exhausted, and specific treatment was stopped. Thereafter the bacteremia increased and the patient developed Type VII pneumococcus meningitis. Serial daily blood cultures showed a steady progression to innumerable colonies per cc. and the patient died on the seventeenth day of his illness. Notwithstanding the fatal termination, it is noteworthy that the blood invasion was reduced from innumerable to less than 1 colony per cc. during serum administration.

No serious serum reactions were encountered in this study. All ophthalmic tests were negative, although a number of moderately positive intracutaneous tests were observed. Fourteen patients had a thermal reaction—usually about 1 hour after serum administration. In 11 of these it followed only the initial dose. In the remaining 3 patients it occurred after 2 successive doses. No ill effects apart from discomfort were observed in connection with these reactions. A chill followed serum administration in only 1 of the 2 fatal cases and did not seem to have any bearing on the outcome. When thermal reactions occurred, they did not seem to have any relation to the lot of serum used, the size of the dose given, or the rate of administration. No salicylates or other drugs were given with the purpose of preventing their occurrence.

Serum sickness occurred in 22 (49%) of the patients who recovered. It became manifest on an average of 11 days after the first dose of serum was administered. In 18 patients urticaria was present, but in only 3 was it extensive or prolonged. Fever occurred in 10 patients, and sometimes continued more than a week. In 12 patients polyarthritis developed, and in 6 it was the dominant feature. Symptoms of mild meningeal irritation were a manifestation in 2 patients. In no cases were the symptoms of serum sickness so severe as to outweigh the apparent beneficial qualities of the serum, or act as a deterrent to the continued use of this method of therapy.

Summary. 1. A report is made on the treatment of 45 cases of pneumococcus pneumonia with homologous type-specific immune rabbit serum. Two deaths occurred in this series.

2. Premature recovery by crisis or rapid lysis ensued in 36 cases.

3. No serious serum reactions were observed.

Most of the patients included in this study were treated with serum supplied by the Lilly Research Laboratories, Indianapolis. The others were treated with serum obtained through the Pittsburgh Department of Public Health.

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THE RESPIRATORY DEFENSE MECHANISM: ITS RELATIONSHIP TO PULMONARY DISEASES.

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UPON injecting lipiodol into the tracheo-bronchial tree by the supraglottic method, it was noted with what ease this could be performed upon 2 cases of lung abscess. It was then decided to test the pharyngeal (gag) reflex of 6 similar cases to determine whether a diminution of these reflexes facilitated the aspiration of lipiodol. Four of the 6 revealed either diminished or absent reflexes. The thought then arose that these abscesses might have partially owed their existence to an inherent defect in this defense mechanism. A study of the various aspects of this protection was then planned and any possible relationship to pulmonary diseases, particularly suppuration of undetermined origin, was to be noted.

The respiratory defense herein alluded to is the purely mechanical reflex protection of the pulmonary system in contradistinction to

biochemical means—as antibodies, opsonins, bacteriolysins, leukins, and so on.²⁹ There are three chief sites—the pharynx, the larynx and the tracheo-bronchial tree—which act as a check valve system to alien material. This action is combined with a propulsive force in an external direction and thus there is a completion of the mechanistic prevention of aspiration. Cough is often associated with these reflexes and in this manner further abets removal. As a matter of fact, it is really the major phase of the bronchial reflex. Although its action is chiefly external, it may also tend to cause a deeper (internal) penetration of foreign material. This can be seen by observing lipiodol in the lungs after cough, and has been studied experimentally by Archibald and Brown,² and others. However, the tracheo-bronchial reflex does not depend entirely on cough, and retrograde peristalsis has been described by Hudson,¹⁰ and Ulmar and Ornstein.³¹ There is a second line of defense if the above safeguards fail. Amberson¹ suggests, in addition to cough as part of the rear guard of the lower respiratory tract, the mechanisms of bronchorrhea, ciliary action and phagocytosis. Defects in any part of the system will allow for easier admittance. Aspiration may take place in other ways in the normal system—as surprise inspiratory blast,²² accidental submersion, and so on.

Material and Procedure. Adults investigated were from the wards of Bellevue Hospital—the Tuberculosis Service and the Third Medical Division. It is well to mention that these patients were from the lower social strata, with poor hygienic standards, a marked tendency to imbibition of alcohol, and exhibiting respiratory foci above average in frequency and degree. Infants and children were studied at the Babies' Hospital in Newark. The normal portion of the control group consisted of private patients, who sought periodic health examinations. The subjects were divided into the following groups:

A. *Control Group.*

1. Normal—no signs of any disease.
2. General medical—all varieties.
3. Chronic lung diseases as tuberculosis, bronchitis, asthma, malignancy, pleuritis, and so on. This last subdivision was chosen to determine whether any chronic pulmonary disease with a persistent cough caused any alterations in the respiratory defense mechanism.

B. *Lung Abscess Group.* Only solitary abscesses of undetermined origin (Fig. 1) were selected. All fell into this clinical classification with a reasonable degree of certainty; some were confirmed by surgery and postmortem examinations. Such obvious suppurations following operations (anesthesia), foreign body aspirations, and so on, were excluded.

C. *Bronchiectasis Group.* All cases were confirmed by lipiodol bronchography (Fig. 2).

Reflexes in each case were tested by the same person (author) in order to avoid any error attributable to an individual variant. However, this still leaves much to be desired, as it is not comparable with methods of machine-like accuracy or precision. The pharyngeal reflex was tested in the usual manner with a wooden tongue depressor and the degree of the gag action was observed. Each reaction was noted as normal, hypersensitive, diminished or absent. The laryngeal reflex, involving closure of the glottis and vocal cords, and propulsive muscular action, was tested by gently touching the laryngeal mucosal surface of the epiglottis with a curved metal applicator. A laryngeal mirror was employed here for observatory purposes. It is to be noted that the number of gag reflexes tested exceeded that of the laryngeal reflexes, for in many of the hypersensitive individuals it was impossible to perform the test or make observations with any degree of accuracy. The tracheo-bronchial reflex was tested in a limited number of cases. It was more complicated, more difficult to interpret and subject to just criticism, because of the indirect method employed. However, for practical purposes, it was deemed of some value. The pharynx and larynx were lightly cocaineized, and lipiodol instilled into the trachea by the supraglottic method. Any coughing was then noted and the patient was fluoroscoped to determine the presence of this opaque body in the bronchial ramifications and its possible expulsion by means other than cough. Of course varied movements of the trachea and bronchi have been described by Jackson,¹² but these are best viewed through the bronchoscope.

In addition to these tests the general neuro-sensitivity of each case was recorded and an attempt was made to correlate the findings with the reflexes. This was determined by the knee-jerk reflex, presence or absence of intention tremors, the general disposition (nervous, normal, phlegmatic) and the styloid test of Libman.¹⁶ Cases were labelled as normal, hyposensitive or hypersensitive on the basis of these tests.

In the suppurative pulmonary groups, upper respiratory foci, pertinent points in the history and other clinical data were recorded, wherever possible. Mouth infections, use of alcohol and sleeping habits were particularly stressed.

As the study progressed, it soon became apparent that not only natural states, but also simple and therefore easily overlooked factors might play important rôles. Therefore, examinations were made under the following altered conditions:

A. Adults During Sleep. Five cubic centimeters of lipiodol were instilled into the mouth or nose of sleeping individuals. Of the 25 cases studied, a nasal catheter to simulate post-nasal drip was employed in 8. In the remaining 17, lipiodol was gently injected into the mouth through a syringe and cannula to simulate oral disease change. Objection may be raised that lipiodol differs somewhat from usual respiratory secretions, but it grossly serves the



FIG. 1.—Lung abscess selected. Cavitation in right upper lobe surrounded by pneumonitis.



FIG. 2.—Bronchiectasis selected, verified by lipiodol bronchography.



FIG. 3.—Adult during sleep. Lipiodol seen in left hilar area.



FIG. 4.—Adult asleep under influence of alcohol. Lipiodol seen in left lower lobe.



FIG. 5.—Adult asleep under sedation. Lipiodol seen in left hilar zone and right lower lobe.



purpose. Roentgen rays were taken within 2 to 5 hours to determine the presence of the oil opacity in the lungs.

B. *Adults Asleep Under Alcoholic Influence.* These patients were not comatose, but could be aroused without difficulty. The same procedure was employed as above.

C. *Adults Asleep Under Sedative Influence.* Again these patients were not comatose, but could be aroused without difficulty. The same procedure was repeated.

D. *Infants and Children (up to 10 Years) During Sleep.* Two to 3 cc. of lipiodol were instilled in the mouth, and Roentgen rays were taken within an hour.

In about 40 cases of the whole series, lipiodol was watched fluoroscopically and checked later by roentgenograms to ascertain the efficiency of the secondary defense.

Results. The following table represents the results of the reflexes tested in the various groups:

Group.	Number of tests.	Site.	Number of reflexes depressed or absent.	Percentage.
1. Total No. tested	650	Pharynx	180	27+
(650 cases)	420	Larynx	70	16+
	66	Tracheo-bronchial	38	57
2. Control group	500	Pharynx	106	21
(500 cases)	333	Larynx	45	13
(a) Normal	75	Pharynx	9	12
	40	Larynx	3	7+
(b) Medical	300	Pharynx	64	21
	225	Larynx	33	14
(c) Chronic lung	92	Pharynx	22	24
	58	Larynx	6	10
(d) Acute	33	Pharynx	11	33
alcoholic	10	Larynx	3	30
3. Lung abscess group (100 cases)	100	Pharynx	57	57
	84	Larynx	30	36
4. Bronchiectasis group (50 cases)	50	Pharynx	12	25
	30	Larynx	3	10

From the above figures it may be reported that 1 of 4 people studied in this series has a depressed pharyngeal reflex and 1 of 6 people has a depressed laryngeal reflex. The various subdivisions harmonize in general with the total sample and the total control group, with two notable exceptions. In the abscess group 1 out of every 2 reveal a deficient protection and in the alcoholic group 1 out of every 3. The tracheo-bronchial reflex, according to our standards, showed an inadequate protection and the most sensitive area seemed to be at the carina—well recognized by others.¹³ In the group of chronic pulmonary diseases there were no alterations in the respiratory defense mechanism and findings were in harmony with the total control sample.

Parallelism of Reflexes. In the whole control group in cases where both pharyngeal and laryngeal reflexes were tested (333 cases),

228 ran parallel. Of the remaining 105, the laryngeal reflex was more sensitive than the pharyngeal in all cases except one. In the subdivisions of the control group and in the suppurative groups similar percentages existed. Thus in the entire series it may be simply stated that in 2 of 3 cases the degree of reaction of both reflexes are the same, and in 1 of 3 cases the laryngeal is more sensitive.

Cough Association. Rather than present each subdivision, it was deemed more satisfactory to review the entire series, for there were no appreciable differences in the groups. Of 650 pharyngeal reflexes tested, cough was elicited in 112 cases (17%). Of 420 laryngeal reflexes tested, cough was an associated action in 155 (36+%). Thus cough was more often associated with the laryngeal reflex.

Neurosensitivity. The entire sample was utilized to determine the correlation of neurosensitivity and reflexes. Of the 620 individuals analyzed, pharyngeal and laryngeal reflexes ran parallel to sensitivity in 457 (73+%), viz.: when the patient was hypersensitive, his reflexes were hypersensitive; when the patient was hyposensitive, his reflexes were diminished. To reduce it simply, in 3 of 4 cases the general neurosensitivity of the patient was an index of the activity of the respiratory defense mechanism. In 1 of 4 cases there was a discrepancy.

Clinical Data on Lung Abscess. Of the clinical notes made in conjunction with the study of the lung abscess group (100 cases) the following data were accumulated:

I. A search for upper respiratory foci revealed the following:		
(a) Pyorrhea	61	
(b) Sinusitis verified by Roentgen ray	9	
(c) Tonsillitis	6	
(d) Upper respiratory infection associated with common cold or grippe	6	
(e) Abscess of tooth	2	
(f) Peritonsillar abscess	1	
(g) No detectable factors	15	
	—	100
II. A clinical study of factors that lead to depression of the reflexes:		
(a) Alcoholic history		63
1. Occasional but light drinker	8	
2. Moderate bouts	41	
3. Coma or semi-comatose states	14	
(b) Non-alcoholic factors		23
1. Fainting spells	2	
2. Epilepsy	2	
3. Cerebral apoplexy	1	
4. Submersion in unclean river	2	
5. Excess sedation	2	
6. Diabetes, non-comatose, but ketogenic state	4	
7. Only possible background—natural depressed reflex state	10	
This last condition was seen in other cases, but the other factor found was given the preference in recording.		
(c) No detectable factors		14
		100

Thus in 100 cases of lung abscess of unknown origin (so-called idiopathic) studied, an etiologic basis could be assigned in approximately 85%. The background consisted of some focus in the upper respiratory tract, especially pyorrhea and some cause for a break in the respiratory defense mechanism—especially alcohol or an inherent state. In the cases where no detectable factors were found, vomitus in alcoholics, and ordinary sleep may further increase the percentage.

Over 50 of these patients were interrogated as to the side they slept on. The majority slept on all sides and therefore, no definite association with the location of the abscess could be made. Of the rest, who favored one side, the correlation was numerically small and, therefore, no conclusion could be drawn. However, it is reasonable to assume that aspiration occurring during sleep favors as the site of suppuration that side upon which the patient is sleeping at the moment. As a matter of fact upper lobe abscess can be explained by the frequency of aspiration in the recumbent position.

The bacteriologic study performed in 30% of the cases is not complete enough to report. Besides, this study has been ably undertaken by others; including Bucher,⁴ Castellani,⁶ Cohen,⁸ and others. The fact that the flora in lung abscess closely identifies itself with various organisms frequently associated with pyorrhea^{5,32} is both interesting and enlightening. The following organisms may be mentioned: Vincent's spirochete, fusiform bacilli, anaerobic streptococci, *Staph. aureus*, *Staph. albus*, *Strep. hemolyticus*, *M. catarrhalis*, *pneumococci*, *B. melaninogenicum*.

Bronchiectasis. In a clinical study of the 50 cases, sinusitis verified by Roentgen ray and with a noticeable post-nasal drip was found in 14. In 7 of these 14 cases there was a natural depression of the respiratory defense mechanism. Therefore, an etiologic background suggests itself in a small percentage of bronchiectasis cases—a break in the respiratory defense mechanism (natural) allowing for aspiration from an upper respiratory focus (sinusitis) causing a more or less continuous infection of the bronchi.

Results of Study on the Respiratory Defense Mechanism Under Altered Conditions (85 tests on 85 cases). A. *Adults during sleep*—4 of 25 aspirated material, as indicated by presence of lipiodol in lung fields, when a Roentgen ray was taken (Fig. 3).

B. *Adults asleep under alcoholic influence*—14 of 25 were positive for aspiration (Fig. 4).

C. *Adults asleep under sedative influence*—4 of 10 were positive as follows (Fig. 5):

1. Salicylate grs. 15 or over—0 of 3 positive.
2. Paraldehyde drams 2 or over—2 of 3 positive.
3. Luminal grs. 1½ or over—1 of 2 positive.
4. Codeine sulph. grs. 1 or over—1 of 2 positive.

D. *Infants and children during sleep*—1 of 25 was positive and this was in a child in a debilitated state.

These figures demonstrate that alcohol and sedation and even normal sleep to a lesser extent tend to depress the respiratory defense mechanism. Sleep under alcoholic influence made one most susceptible to aspiration. Children seemed to have a potent respiratory defense mechanism. They were not tested under alcoholic and sedative influences, as these are negligible factors.

During the sleep problems it was noted that the unpleasant taste of the lipiodol, the handling during the injection and the previous apprehensive state of the patient at times were disturbing. For the oral injection, people who were mouth breathers were selected because of easier accessibility. Incidentally, it seemed that this last class tended to compensate for any nasal obstruction by a greater depth of inspiration. This possibly made them more prone to aspiration from the upper passages.

Observations made on these sleeping individuals seemed to indicate other means of protection besides the respiratory reflexes. Some would swallow the oil, others spat out the foreign substance without waking up; drooling of oil and saliva from the side of the mouth was also noted. Several coughed, but kept on sleeping. About 25% were awakened by the procedure. In children, despite the fact that all slept right on, only 1 showed a small amount of oil in the lungs. The outstanding protective mechanism in the majority was swallowing (Fig. 6), thus shunting off alien material from the respiratory tract. This seemed to be a highly developed reflex in infants. It is not an uncommon sight to see an infant, apparently asleep, feeding at the mother's breast.

Secondary Defense Mechanism. Results of studies in the 40 subjects after lipiodol injection seemed to indicate that the first few minutes comprised the active phase. Coughing and retrograde peristalsis were most active then. After the first few minutes (5 to 10) there was a second or dormant phase. The lipiodol remained in the lungs without much movement and could be observed for days thereafter. This is a rather gross index of the lack of complete efficiency of the rear guard.

Comment. A study of the respiratory defense mechanism reveals the laryngeal reflex as the real "watch dog" of the lungs. The pharyngeal reflex might be regarded as the vanguard and the tracheo-bronchial system brings up the rear guard. Once ordinary fluid substances (as respiratory secretions) pass the larynx, the possibility of retention and subsequent damage is increased. Although there are modes of dealing with foreign material in the lower tract, the protection is not completely adequate and undoubtedly a small percentage goes on to a definite pathologic condition. Cough is an important associative phase of all respiratory reflexes;

but it is not present at all times. Particularly is it wanting when we are not dealing with coarse physical objects or those capable of causing chemical irritation. With the more bland and fluid substances its absence is often noted. The fact that cough is more often associated with the laryngeal than the pharyngeal reflex, tends to make the former more important.

It is very essential to avoid anything which will depress all these reflexes. Unfortunately, in a minority of cases an inherent condition of lowered sensitivity exists. This has been reported by Jackson and Coates¹⁴ and others. Although this depressed state may be protective during conscious periods, the addition of sleep tends to create a problem and no artificial means should be permitted to deepen the sleep.

As shown by the study of the respiratory defense mechanism under altered conditions, alcohol and excess sedation definitely raise the threshold of reaction. In the past both have been employed in upper respiratory infections—at times without moderation. This undoubtedly is a mistake and, from a practical point of view, the physician must be cautioned even in such ordinary conditions as colds and gripes, but particularly in septic mouths. The use of alcohol in these conditions has been advocated by trade magazines²¹ distributed to the physicians. Jackson¹² many years ago said that if the reflexes are not drugged asleep, protection is usually present.

The results of the study in the abscess group brought out many interesting facts and possibilities. Over 50% of the cases possessed a native depressed state of reflexes and this undoubtedly contributes to the pathogenesis. Among the factors tending to drug the mechanism, the alcohol habit predominated. If a careful history is not taken, this point may be overlooked, for comatose or even semi-comatose states are not necessary. Unless sought for, one may overlook other factors as fainting spells, epilepsy, submersion and pre-comatose states (including ketosis). In diabetes, untreated or inadequately treated, two factors are at play—a decrease of reflexes during acidosis and a higher susceptibility to infection.

It is not within the scope of this paper to discuss postoperative abscess following anesthesia, but here a break in the respiratory defense mechanism must assume the dominant rôle. Of course, the protagonists of the embolic theory offer very attractive theses. However, it is reasonable to assume at present that both avenues offer possibilities. Because of this study the aspiratory theory is favored in the majority of cases.

As for upper respiratory foci in this suppurative class, pyorrhea is by far the most common offender, though it is recognized that this is a common condition, especially in the class of people here studied. Sinusitis, tonsillitis and tooth infections must also not

be overlooked. The frequency of diseased mouths in association with lung abscess has been recognized by many, including Marietta,¹⁷ and Stern.^{27a,b} The latter found the condition present in 84% of pulmonary abscesses of unknown cause that he studied.

In the past many cases of lung abscess, although recognized clinically, have been baffling from a viewpoint of pathogenesis. Often the abscess has been improperly considered a sequela of lobar pneumonia; when as a matter of fact the pneumonitis is part of the pathologic picture. Both American^{29,30} and foreign observers²⁶ attest to the fact that the etiologic basis is not often clear. However, if one bears in mind and searches for two factors—namely a focus of infection in the upper respiratory tract and an explanation for the transient or permanent defect in the respiratory defense mechanism—the mystery of pathogenesis is soon unveiled and the term “unknown” may be greatly restricted. Of course, a small percentage, as in this series, escapes all means of detection; but the mechanism is undoubtedly the same. The facility with which material from the mouth and pharynx is aspirated in the lungs, has been demonstrated by numerous investigators, as Mullins and Ryder,²⁰ Lemon,¹⁵ Meyerson¹⁹ and Iglauer.¹¹

Our series demonstrates as an important triad in lung abscess and therefore worthy of repetition—alcohol, a naturally depressed respiratory defense mechanism, and pyorrhea.

This series revealed a sex incidence of approximately 3 males to 1 female, and an age incidence, which appears to spread over wide limits with a marked preponderance in middle life. This harmonizes with the larger series of Maxwell¹⁸ and others. This can possibly be explained by the more frequent occurrence of pyorrhea and use of alcohol in males and in middle life. In addition, the female patient is more nervous and therefore tends to have a better respiratory defense mechanism. Early and prompt dental care are prophylactic considerations. One can truly describe the average abscess individual as “a middle aged male, pyorrhetic with a tendency to bouts of alcohol.”

The infrequency of lung abscess in infants and children can be explained by a better respiratory defense mechanism and a relative infrequency of upper respiratory factors, particularly pyorrhea. Smith²⁵ in a review of American literature collected only 59 in children among 2250 cases of abscess. It was interesting to note that aspiration in the sleeping children occurred only once and then in a debilitated child. Debilitation is not only a factor in lower resistance to infection, but also in facilitating aspiration. The case report by Sullivan²⁸ describing aspiration of barium in a debilitated person bears out this fact.

In premature and ill children, where debilitation is pronounced, aspiration bronchopneumonia is not uncommon. This is associated

with a process of regurgitation and no upper respiratory factor need be present.

Vomitus, instead of upper respiratory infection, may be the other factor in adults, who are in a weakened condition. Because of gastro-intestinal disturbances in alcoholics, this mechanism may particularly assume the rôle here.

A mechanism similar to that described in the production of abscess is also possible in other diseases. Bronchiectasis is one which this study exposed as being a potential menace to people with inherently depressed respiratory reflexes and upper respiratory infections. There are many other causes of this disease, ably described in the literature. Association of bronchiectasis and upper respiratory infections, including sinusitis, has been recognized by Sergent, *et al.*,²⁴ Graham, *et al.*,²⁵ Clerf⁷ and others. However, no literature was found indicating as a basis for aspiration from the upper passages in this disease a native state of susceptibility.

Other diseases, such as pneumonia, bronchopneumonia, suppurative pneumonitis, and even bronchitis may also be attributable to this mode of pathogenesis. Further studies are necessary to warrant a definite opinion. The comparatively high carrier rate of pneumococci in persons with infections of the upper respiratory tract is being appreciated and studied because of the epidemiologic significance. Although strains carried are representative of those least often found in pneumonia, a certain percentage, particularly among family contacts,³ may show a high degree of pathologic strains. Here we have the upper respiratory factor in a rather innocent form. As soon as a break in the respiratory defense mechanism occurs in these cases, the background for the disease presents itself. Only recently a paper by Nungester, *et al.*²³ was presented and in it a similar mechanism was suggested in pneumonia when alcohol drugged the reflex system. This was experimental work carried on in animals. In general, it is reasonable to assume that the disease produced depends in great measure on the flora and symbiosis of organisms aspirated.

Summary and Conclusions. 1. The respiratory defense mechanism has been discussed and the three sites for checking aspiration noted—the pharynx, the larynx and the tracheo-bronchial tree. The larynx was the most sensitive and the tracheo-bronchial tree seemed least effective when fluid media were the vehicles. The parallelism and interrelationship of these reflexes were discussed, including the association of cough with each.

2. A deficient mechanism plus some focus in the upper respiratory tract were regarded as the cause for certain pulmonary diseases. This break may be an inherent part of the individual's makeup or caused by such factors as alcohol; sedatives, pre-comatose states (diabetes) and so on.

(a) Idiopathic lung abscess especially falls into this group and was discussed from several angles. Alcohol, a natural depressed state of respiratory reflexes, and pyorrhea furnish the important triad.

(b) A certain percentage of cases of bronchiectasis can be explained on basis of a depressed respiratory defense mechanism when upper respiratory foci are present.

(c) The possibility of relationship of a similar mechanism to other diseases, as pneumonia, bronchopneumonia, and so on, is stressed.

3. Prophylactic Views: (a) The treatment of all upper respiratory foci, including infections of teeth, tonsils, gums, and sinuses, is important.

(b) The presence of all factors that tend to drug the respiratory defense mechanism must be avoided.

(c) Special efforts should be made to clear efficiently and early all upper respiratory infections in people with an inherent break in the respiratory defense mechanism as they are most prone to aspiration infection of the lungs.

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STUDIES ON OXYURIASIS.

XVIII. THE SYMPTOMATOLOGY OF OXYURIASIS AS BASED ON
PHYSICAL EXAMINATIONS AND CASE HISTORIES ON
200 PATIENTS.

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THE rather amazing incidences of *Enterobius* [*Oxyuris*] *vermicularis* found in surveys conducted by workers in our laboratory and reported by Cram, Jones, Reardon and Nolan¹ have stimulated our interest in the symptomatology of oxyuriasis. Insofar as we can determine by a survey of the literature, no effort has been made in the past to study this condition as a clinical entity and to delineate on the basis of an examination of a sufficient number of cases symptoms which may be definitely linked with pinworm infestation. While some authors have expressed the opinion that this ubiquitous parasite may be of considerable medical importance, the more prevailing attitude seems to be that the pinworm is a rather innocuous parasite and that pinworm infestation is a condition requiring little or no attention from a therapeutic standpoint.

Our survey is based on case histories and physical examinations of 200 patients who came to us either through a clinic at Providence Hospital, Washington, D. C., or were referred to us by practicing physicians. These 200 cases consisted of persons seeking treatment for known pinworm infestation, persons referred to us because of symptoms suggestive of oxyuriasis, and persons found positive for pinworms on anal swab examinations made during incidence studies.

For comparison with these 200 cases we have two groups of controls divided into classifications, as follows: One group of 72 persons negative for pinworms on examination by the NIH swab described by Hall⁴ but dwelling in households in which infested individuals were present, and a second group of 21 persons negative for pinworms and living in homes in which no member of the family was found infested. Since individuals in our first group associated with infested individuals, the possibilities for their infestation are patent and their use as a control group is subject to criticism. Individuals in the second group, admittedly too few in number, may probably be regarded as free from pinworms. In the group of 72 persons negative themselves on swab examinations but living with infested persons, there was an average number of 4.9 swabs made for each person. It has been our experience that if these persons are swabbed for long periods of time almost all would be found to be intermit-

tently positive on swab examinations. It is because of this intermittent infestation that the second group of 21 persons were used. These were found negative on an average of 4.1 swab examinations and came from households having all members negative on swab examinations. We believe it is very unlikely that any of these persons would be found to have a positive swab on a long series of swab examinations. The facts above-mentioned and the fact that our controls were not selected on a basis of random sampling somewhat weaken the results of our survey and lend caution to our conclusions.

In the case of adults, the case history was obtained from the patient while in the case of children the information was furnished by the parent, usually the mother. Rough hemoglobin determinations were taken on most of the patients by the Tallqvist method and differential blood counts were made in a majority of cases. A stool specimen from each patient was examined by the salt flotation method, and patients found to be harboring intestinal helminths other than pinworms were not considered in this study. At the time of the physical examination, a vulvar swab was made on girl patients, the swab being taken at the introitus and effort made to avoid touching the skin.

We believe that the pinworm can cause symptoms in at least 3 ways, *viz.*, by mechanical stimulation and irritation, by an allergic action, and by the transportation of organisms, usually non-pathogenic, to places where they may become pathogenic. Such general symptoms as decreased weight and pallid complexion, which may be due to absorption of pinworm toxins, have not been found to be correlated with the intensity of infestation but appear to be conditioned only by the presence of pinworm material.

There is some evidence in the literature that pinworm material may cause allergic manifestations. Heubner⁵ commented on the frequency of sneezing in oxyuriasis. Leibholz⁶ noted pruritus and eczema of the lower half of the body which he thought was probably due to a pinworm allergy. Morénas⁷ and Götz² cited cases with allergic symptoms which they attributed to pinworms. Grübel,³ Schröpl⁹ and Wright and Bozicevich¹¹ reported results of skin tests with pinworm antigen and found a considerable degree of specificity.

General Symptoms. This series of cases showed no anemia attributable to pinworm infestation. Wright, Bozicevich and Gordon¹² found that many underweight children showed considerable gains in weight after treatment. We were impressed by the large number of infested children showing dark circles under the eyes and a pallid facies in spite of a normal hemoglobin determination. These cases showed remarkable improvement in their complexions after treatment.

Eosinophilia. Differential blood counts were made on 144 of the infested individuals and on 21 control cases. These controls were

carefully selected as to freedom from parasitism and were cases coming from households free from pinworms. Two hundred leukocytes were counted in all cases. The average percentage of eosinophil cells in the infested group was 5.1% and the average in the non-infested group was 3.7%. In both series there was considerable deviation from the mean, and comparison does not show the difference in percentage to be of statistical significance. The analysis of a larger series very likely would show that a slight eosinophilia exists with pinworm infestation. There appeared to be no correlation between the degree of the infestation and the increase in the number of eosinophils.

Gastro-intestinal Symptoms. In 1 case there was a history of nausea and vomiting occurring between 5.00 and 6.00 A.M. on the average of twice a week. It is known that this individual did not have pinworms prior to the onset of these complaints. The patient was treated about 6 weeks after the onset of these symptoms and, with eradication of the infestation, the symptoms disappeared. The history and physical examination showed no other cause for these complaints. It is interesting to note in this connection that Pétrovykh⁸ reported on 3 patients having gastro-intestinal complaints and from whom pinworm larvæ were recovered in duodenal washings. These symptoms subsided after eradication of pinworms. Prior to the finding of the larvæ, the clinical diagnosis in 1 case was peptic ulcer and in the other 2 cases was biliary tract disease.

Abdominal pain was about as frequent a complaint in persons in the control group as in persons in the infested group. In this series of cases but 1 case had had an appendectomy. We found no evidence in our cases that oxyuriasis was related either to acute or chronic appendicitis. We feel that pinworms found in appendices removed by operation represent usually a chance finding and in most cases are not related to the disease condition found. In fact, with the apparent high existing incidences of oxyuriasis, it is surprising that more surgically removed appendices do not contain pinworms.

Anorexia was a common complaint in infested children and in many cases the appetite was much improved after treatment for pinworms. Craving for sweets was found as frequently in patients in the control series as in patients in the infested group.

Although many individuals of a phlegmatic temperament and many of those having infestations over a long period of time frequently denied experiencing any sensation from migrating pinworms, it is apparent that the majority of people are aware of a sensation, varying in intensity from a very mild tickling to a sensation of acute discomfort that may be described as pain when the females are yet on the rectal and anal mucosa. It is believed that this sensation is due to a mechanical action of the migrating worm. Skin sensation is uncommon but it may be very marked in the few individuals who experience it. It seems probable that the sensory nerve endings

of the skin cannot ordinarily detect the sensation of a moving pinworm and it is believed that this symptom must be explained on some other basis. One patient, a middle-aged woman, stated that during migrations the skin along the tract of the migration would become intensely itchy and the pruritus would cease only after careful scrubbing of the area with soap and water. This patient stated that she frequently experienced migrations while playing bridge in the afternoons and on such occasions she would have to excuse herself and take a bath in order to alleviate the extreme pruritus. A male, 32 years of age, not only complained of the perianal itching with migrations but stated also that he experienced itching elsewhere on the skin when migrations occurred. In such cases as these, it is believed that the individuals are distinctly allergic to pinworm material.

Genito-urinary Symptoms. Enuresis has frequently been attributed to pinworm infestation. We were unable to show that enuresis occurs with any greater frequency in infested individuals than in our group of non-infested controls.

Our observations indicate that migrating females very frequently enter the vulva. Shulman and Paretskaya¹⁰ stated that one observer saw 16 of 43 migrating pinworms disappear between the labia. Mothers have frequently told us that in girls the pinworm is more likely to migrate in the direction of the vulva than elsewhere. Of 45 cases in young girls, 14 (31%) were positive on one vulvar swab made at the introitus. This percentage agrees with the expectancy of positive cases disclosed by one anal swab. In 2 of these cases the vulvar swab was positive while a perianal swab made at the same time was negative. Ten of the 51 girls examined showed a mucoid vaginal discharge. We are of the opinion that the discharge in most of these cases was due to irritation of the genital tract from parasites migrating between the labia and into the vagina. It is reasonable to assume that with the high incidence of oxyuriasis and our evidence that pinworms frequently reach the vagina, there exist many cases of vaginitis due to pinworms that are not diagnosed as such. It is possible also that some cases of purulent vulvovaginitis may be due to organisms carried into the vagina by migrating pinworms. If desiccation is the stimulus that initiates oviposition and the death of the migrating female pinworm, as observations indicate, it is understandable how the female pinworm can remain viable and migrate into the uterus, tubes, and peritoneal cavity, since in reaching these locations it traverses a moist channel not conducive to loss of activity. However, we had no cases in this series in which evidence indicated that pinworms had migrated to these locations.

Nervous Symptoms. Restlessness at night is common among pinworm patients and can be attributed to the annoyance caused by the migrating worms. Insomnia may occur, particularly in

adults. In more heavily infested cases there may be migration during the day with accompanying restlessness. One of our patients, a girl of 12, experienced frequent migrations during school hours. Her teacher complained of her lack of coöperation and inattention. This girl also had personality changes due to a feeling of shame and inferiority from the knowledge that she had pinworms. She was subjected to ridicule by her playmates because of her constant scratching of the perianal region.

We were unable to show that nail biting, thumb sucking, nose picking, and grating the teeth were more common in the infested group than in the control group. The more abstract manifestations of nervous irritability such as reflex changes, emotional changes, and changes in temperament were too difficult of evaluation to enable us to arrive at any conclusions concerning them.

Summary. Two hundred cases of oxyuriasis were studied with a view of ascertaining the symptomatology of this condition. In each case a history was taken, a physical examination was made, a stool sample was examined for helminth ova, anal swabs were made, and in girls, a vulvar swab was made. The opinion is expressed that symptoms may be caused by mechanical stimulation and irritation by the parasite, by allergic reactions, and by the transportation of organisms to places where they may become pathogenic.

Many infested children showed gains in weight, improvement in color, and disappearance of dark circles under the eyes after treatment.

There was an average eosinophil percentage of 5.1% in 144 pinworm cases compared to 3.7% in 21 children coming from households in which all individuals were free from pinworms. There is too much deviation from the mean for these figures to assume statistical significance, but it is likely that there is a slight increase in eosinophil percentage in oxyuriasis.

One case presented symptoms of nausea and vomiting that could not be attributed to causes other than the pinworm infestation. These symptoms disappeared when the pinworm infestation was eradicated. We found no proof that abdominal pain and oxyuriasis were directly related. Only 1 case of the 200 had had an appendectomy. The appetite in many cases was much improved after treatment.

It is believed that pinworms cause conscious sensation when moving on the rectal and anal mucosa, but that no sensation is felt in the majority of cases after the pinworm has migrated onto the skin. Allergic reactions to pinworm products are probably associated with the very marked sensation experienced by some few individuals from skin migrations.

Enuresis was not found to be more common in infested patients than in non-infested controls. Evidence is presented that a pinworm vaginitis may be much more frequent than it has been considered to be in the past.

Restlessness and insomnia are symptoms occurring in pinworm cases. Restlessness in school may lead to scholastic difficulties. The feeling of shame that an impressionable child may have from the knowledge that he or she has pinworms may have repercussions in the behaviorism of the child. Evidence to show that pinworms cause nervous irritability was inconclusive.

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THE PLATELETS IN PERNICIOUS ANEMIA.

WITH A REVIEW OF THE LITERATURE.

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ALTHOUGH it is generally accepted in the current textbooks that the platelets are diminished in pernicious anemia, there has been relatively little published work on the subject. That a low platelet count is a necessary part of the disease in its more severe stages was apparently first recognized by Hayem in 1889, who found the platelets below 100,000 per c.mm. in 3 of 4 cases. Various authors since^{4,7,12,14,19a,25,27,32,34} have mentioned this change, those giving specific figures being listed below. The platelets have even been reported as being entirely lacking.²⁸

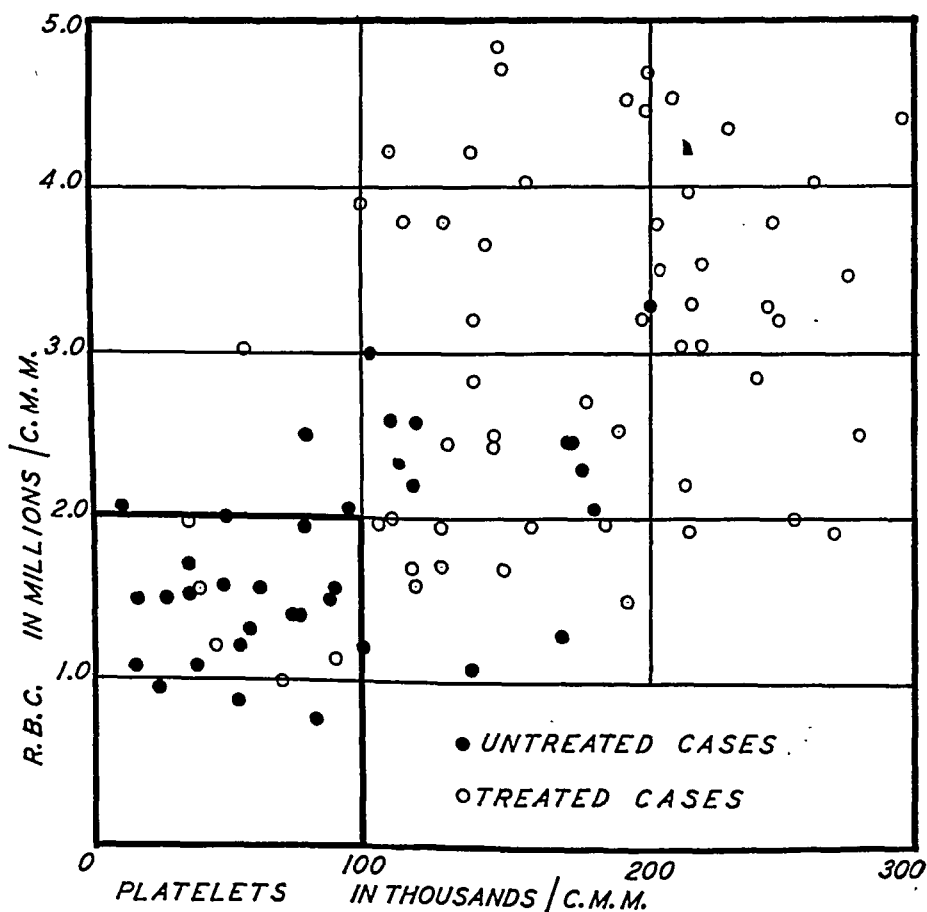
Methods. We have reviewed all the cases of pernicious anemia in the Presbyterian Hospital in the city of New York on whom platelet counts were done. All of these responded classically to the administration of liver and have since maintained their counts on this regime.

Blood taken directly from the patient's fingertip was drawn into a standard red cell counting pipette to the 0.5 mark and diluted 200 times by addition of 3% sodium citrate solution freshly prepared each morning. The diluted blood, after shaking, was then placed in a standard blood counting chamber and the platelets within the central square millimeter were counted, the final figure being multiplied by 2000, thus giving the

number of platelets per c.mm. of blood. All of the counts were done by three trained technicians in the Hematology Laboratory during the past several years.

Author.	Year.	No. of cases of severe anemia with platelets below 100,000 per c.mm.	No. of cases of severe anemia in which platelets were counted.
Hayem	1889	3	4
Minot	1918	1	1
Degkwitz	1919	1	1
Gram	1920	16	24*
Allard	1926	7	8
Kristenson	1930	12	15
Nittis	1931	5	6
Dyke	1931	3	3
Segerdahl	1932	1	1
Arneth	1937	30	30*
		<hr/> 79	<hr/> 93

* Specific red cell counts not given.



GRAPH 1.

Results. In all we have assembled 90 simultaneous red cell and platelet counts on patients with pernicious anemia in our records,

of which 36 were initial counts on untreated cases. All of these we have placed in the accompanying graph (Graph 1), plotting their erythrocyte counts against their respective platelet counts. As can be seen, the thrombocyte count in general varies directly with the height of the red cell count. Of the 22 cases of untreated anemia with a red cell count of 2,000,000 per c.mm. or less, only 2 cases had a platelet count of more than 100,000 per c.mm.; that is, the finding of a severe anemia without a coincident thrombocytopenia is, according to our series, uncommon.

Discussion. Manifestations of the diminished platelet count are not recorded in the original paper of Addison,¹ but Biermer⁶ in his initial description of pernicious anemia in 1871 pointed out the high incidence not only of retinal hemorrhages and small cutaneous petechiæ, but also the occasional presence of marked gastro-intestinal and genito-urinary bleeding. The presence of purpura and a poor retraction of the blood clot has also been emphasized by other authors.^{11,15,17,19b,22,28,30,32}

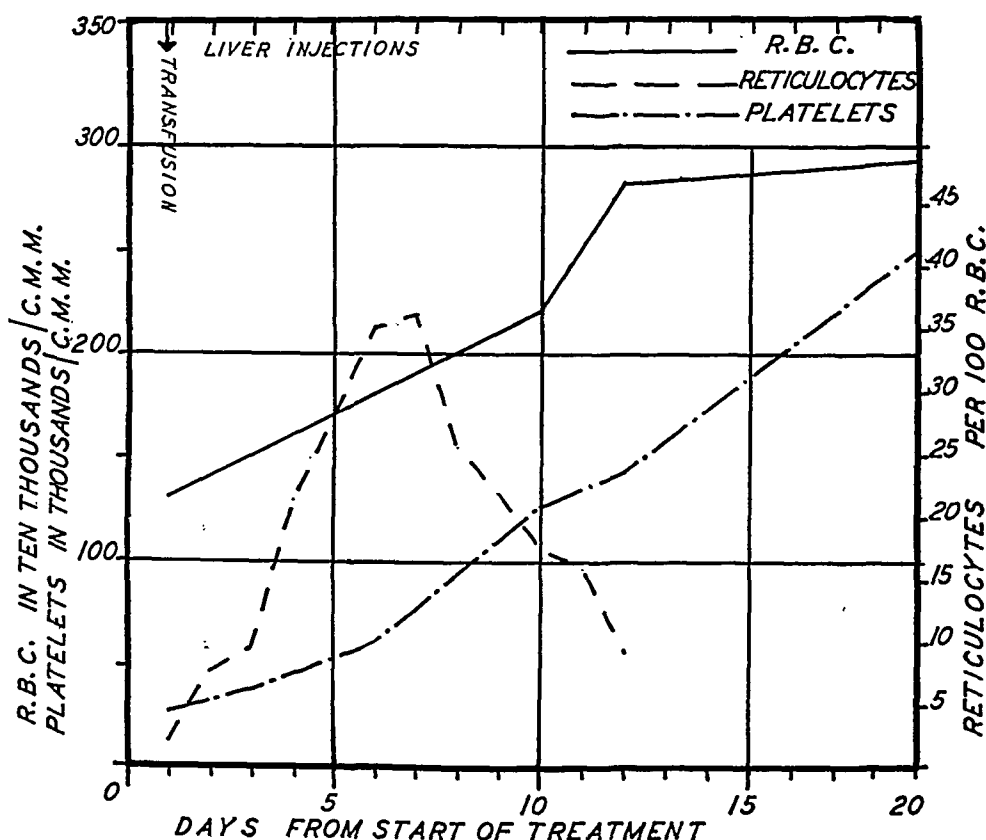
TABLE 1.—PLATELETS IN PERNICIOUS ANEMIA BEFORE AND AFTER TREATMENT.

Patient.	Before treatment.		After treatment.		Continued treatment.	
	Plts.	R.B.C.	Plts.	R.B.C.	Plts.	R.B.C.
1	16.0	1.5	150.0	4.8
2	18.0	1.1	193.0	2.6		
3	26.0	0.9	41.0	1.6	214.0	4.6
4	27.0	1.3	241.0	2.9		
5	28.0	1.5	56.0	3.1
6	48.0	1.6	36.0	1.9		
7	58.0	1.3	183.0	2.7	131.0	3.8
8	74.0	1.4	219.0	3.3
9	76.0	1.4	140.0	3.2
10	82.0	0.8	90.0	1.1		
11	89.0	1.5	280.0	2.5		
12	114.0	2.3	247.0	3.3		
13	139.0	1.1	259.0	2.0	110.0	4.2
14	171.0	2.4	147.0	3.6
15	172.0	1.3	296.0	4.4
16	180.0	2.3	248.0	5.6
17	119.0	1.7	263.0	4.1
18	120.0	1.6	249.0	3.8
19	196.0	1.5	206.0	4.4
20	202.0	3.2	218.0	3.9

(Platelets recorded in thousands per c.mm., red cells in millions per c.mm.)

Numerous papers,^{2,12,15,17,18,23,24,33} particularly before the advent of liver therapy, have stressed that in spontaneous or induced remissions of the disease the platelets show a marked and prolonged rise, sometimes even before the reticulocyte response particularly if the remission is well sustained. The platelets may, indeed, with the commencement of specific therapy even rise markedly above normal, as high as 1,225,000 per c.mm. having been reported;²³ no thromboses, though they might be expected on this account, have been reported. In our experience, the rise of the platelets is in general coincident with the rise of the red cell count and may reach

a higher level at the beginning of therapy than when the red cell count approaches normal. These points are illustrated in the accompanying table (Table 1) with a graph (Graph 2) of a specific case.



GRAPH 2.

A study of the different types of the platelets reveals that in the severer stages of the anemia there is a predominance of the small forms with occasional giant and other abnormal forms.^{3,24,25,28}

Unfortunately, this diminution in the number of platelets is apparently of little use in differentiating pernicious anemia from other macrocytic anemias. In sprue at least one-half of the patients with a macrocytic blood picture have also a marked thrombocytopenia.^{5a,b,29} In carcinoma with a macrocytic anemia the platelets may be diminished,¹⁶ but little work has been reported on this subject. Franco, in 8 cases of carcinoma of the stomach with the red cell counts for the most part above 2,000,000 per c.mm., found the platelets little diminished if at all.¹³ In the leukemias the platelets may be either normal, diminished, or augmented, varying with the type and duration of the disease.^{9,20} In the macrocytic anemia

of pregnancy we have found cases with a low platelet count. Cirrhotics with a macrocytic anemia, not only in our experience, but in that of others,²¹ may show a thrombocytopenia.

Summary. 1. In marked pernicious anemia a definite thrombocytopenia is rarely lacking. This is borne out not only by our own figures of 90 counts, but by those collected from the literature.

2. The platelets increase in number parallel to the red cell count on the institution of specific therapy.

3. This diminution of platelets is apparently of no value in differentiating this type of anemia from others with a macrocytosis.

We are indebted to Miss Illyne and Miss Whipple for their kind coöperation.

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ERYTHROBLASTIC ANEMIA

REPORT OF TWO CASES IN ADULT SIBLINGS. WITH A REVIEW OF THE THEORIES AS TO ITS TRANSMISSION.

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IN 1927 an important step was taken by Cooley^{3,4} who separated from the hemolytic anemias of childhood a sub-group which he called erythroblastic anemia.

The essential features of this disease are as follows: It occurs in early childhood and is usually fatal within a few years of onset. Clinically, it may be recognized as early as the third month, and Roentgen ray changes have been noted as early as the fourth month.¹ It occurs only in children whose parents have their origin in the Eastern Mediterranean area and no cases reported as arising in peoples of other geographic regions have been substantiated. (One case originally cited by Cooley as having a British parentage was later proven to be a true congenital hemolytic icterus.^{2a})

The course of the disease is characterized by bouts of fever, which may be constant, intermittent or undulant; great enlargement of the spleen; an icteric tint to the skin and scleræ but without bile in the urine; and certain blood and bone changes which will be described in greater detail.

Blood. The blood is characterized by an anemia with an average hemoglobin of about 36% and red blood cell counts of 2,900,000. It is of the hypochromic microcytic type. The outstanding feature is the presence of large numbers of erythroblasts, with rare megalo-blasts. After splenectomy, which is not curative, a striking increase in the erythrocytes occurs. The neutrophils are invariably increased, but to a moderate degree. Many myelocytes can also be found. Wet preparations reveal marked fragmentation but no sickling. In short, there is a marrow hyperplasia which floods the blood stream with immature and atypical cells, chiefly of the red series.

Red Cell Fragility. One of the constant features of the disease which is of differential importance in separating it from congenital hemolytic icterus is the increased resistance of the red cells to hypotonic salt solutions.

Skeletal Changes. The bone changes consist of an enlargement of the spongiosa of the bone with thickening of the internal table and almost complete disappearance of the external table. There is a replacement of the marrow by bony tissue, which gives the peculiar striated picture characteristic of this disease. The thickening and replacement of the marrow with bone which occur late, are thought to be compensatory to the weakening caused by the osteoporosis which is an early finding.

Changes in the long bones and flat bones are more constant than those in the skull but it is the latter which gives the striking appearance of mongolianism to these children (Fig. 4). All the bones of the skull may be involved but it is particularly noticeable in the frontal and maxillary bones. One gets a peculiar sense of thickness and solidity on palpating the face of these children. An excellent summary of the skeletal changes with a bibliography of erythroblastic anemia can be found in an article by Caffey.¹

Theories as to Etiology. Cooley⁴ thinks the disease must be congenital but, in spite of its frequent familial occurrence, he rules out heredity because the reported cases all died before puberty and, therefore, before they could transmit it to their offspring.

Whipple and Bradford⁷ who have studied several cases carefully from the pathologic standpoint, including two in identical male twins, believe it to be an inherited defect involving the hematopoietic and osseous systems. They believe it is due to a deficiency either of a vitamin or endocrine nature, acting in a manner comparable to the defects in pernicious anemia, scurvy or acromegaly.

Whipple and Bradford⁷ think the bone defects are specific and not simply secondary to marrow hyperplasia, since in the hyperplasia of long standing pernicious anemia or leukemia similar changes are not found.

These investigators also point out the interesting fact that erythroblastic anemia has a peculiar pigment distribution in the tissues that is duplicated in only one other disease, namely, hemochromatosis.

Other authors have confused erythroblastic anemia with von Jaksch's anemia, and some with chronic malarial splenomegaly.

Therapy. Whipple and Bradford⁷ tried numerous therapeutic agents and, in spite of adequate dosage, found their value entirely negative. They gave a thorough trial to blood transfusions, plasma and cell extracts, raw pancreas, adrenal cortex (cortin), estrogenic substance and iron and copper.

Roentgen ray therapy has been advocated by Hunter⁵ but the results do not warrant the risk of developing a severe aplastic anemia such as occurred in one of his cases. So far there have been no favorable permanent results from radiation.

Caminopetros^{2b} noted the benefit which occurred in a case having a coincidental infection with malaria and thereupon inoculated 7 other patients with the disease. The results led him to believe that malarial therapy was as effective as that of Roentgen ray in leukemia. He found a reduction of the number of abnormal erythrocytes circulating in the peripheral blood and the development of a leukopenia. The parasites were almost never found in the altered red blood cells, a fact which the author believes is associated with their increased resistance and an absence of chemotaxis. In view of the small number of cases in which malarial therapy was used and the absence of any data regarding their later progress, it would seem wise to withhold judgment until there is further substantiation of this as a cure.

It has been our good fortune to follow two patients in one family over a period of 12½ years. Their histories are as follows:

Case Reports. CASE 1.—D. P., aged 20, was first seen in 1926 at the age of 8. Her complaints were weakness, yellow color and a mass in the abdomen. She had been a full term baby, with adequate feeding. At the age of 2 years she had had numerous nose bleeds but otherwise her history was uneventful, except that her color differed from other children and that she seemed apathetic. Her mother noticed that the muddy yellow color of the skin and sclera varied in intensity from time to time.

Physical examination was negative except for the peculiar color mentioned above and the presence of an enlarged spleen. This reached to the iliac



FIG. 1a.—D. P. Skull, 1932.

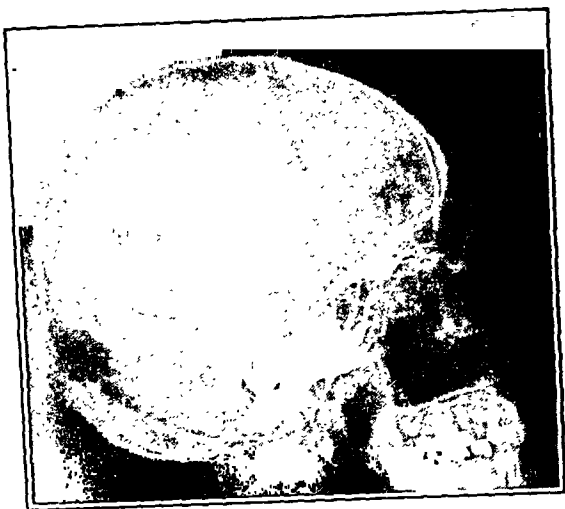


FIG. 1b.—D. P. Skull, 1938.

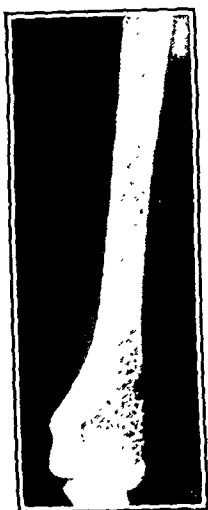


FIG. 2a.—D. P. Humerus, 1932.

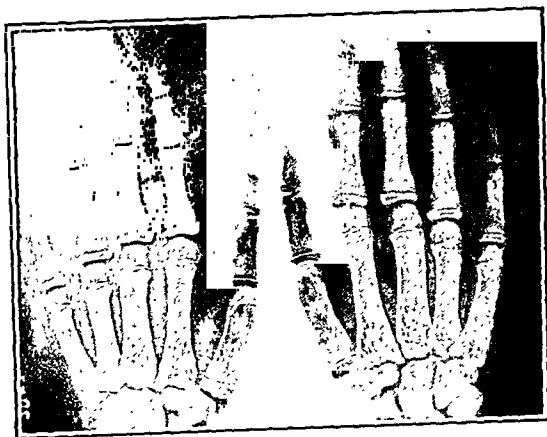


FIG. 2b.—D. P. Hands, 1932.



FIG. 3.—S. P. Chest, 1938.



FIG. 4.—S. P. Age 17. Front view.



FIG. 5a.—S. P. Skull, 1928.



FIG. 5b.—S. P. Skull, 1932.

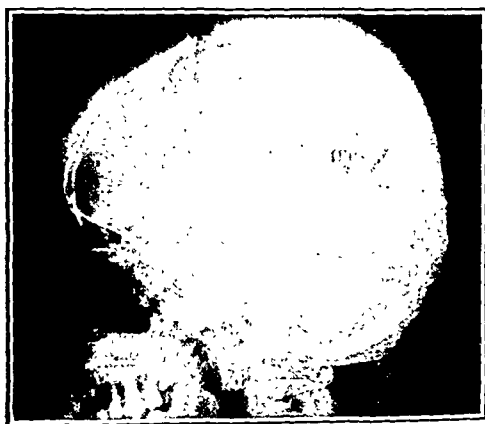


FIG. 5c.—S. P. Skull, 1938.

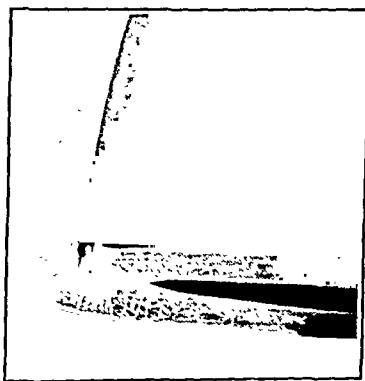


FIG. 6a.—S. P. Humerus, radius and ulna, 1932.



FIG. 6b.—S. P. Pelvis, 1932.



FIG. 6c.—S. P. Pelvis, 1938.

crest and nearly to the midline. It was firm and had a sharp notched margin. The liver was palpable just below the costal margin and in the epigastric notch.

Laboratory Data. Hemoglobin 45% (Sahli); erythrocytes 3,900,000; leukocytes 9620; differential count: neutrophils 59%; lymphocytes 37%; monocytes 3%; myelocytes 1%; nucleated red cells 4%. The smear showed microcytes and tailed cells, with a few macrocytes. There was some stippling. Red cell hemolysis in hypotonic salt solutions began at 0.375 and was not complete at the lowest dilution, 0.025. The urine was negative for bile. The Wassermann test was negative.

The child did fairly well, able to attend school and partake in the usual physical activities of childhood. However, from time to time she lagged a little, usually when the family, who were on relief, found it difficult to provide adequately nutritious food. At such times she would be sent to a convalescent home or hospitalized. Further studies at these times were as follows:

June, 1932. Hemoglobin 50% (Sahli); erythrocytes, 4,300,000; leukocytes, 6120; platelets, 240,000; average diameter of red cells, 7.2μ ; reticulocytes, 2.4%; normoblasts, 6%; bleeding time, 2 minutes; fibrin formation, 2 minutes. The phenolsulphonphthalein test showed an output of 75% in 2 hours. The urine was negative for hematin. The icterus index was 18.75. Cholesterol: 85 mg. per 100 cc. of plasma. Calcium: 10.1 mg. per 100 cc. of serum. Inorganic phosphorus: 4.75 mg. per 100 cc. of serum.

A biopsy of the sternal marrow (Dr. J. L. Carr, Pathologist) revealed normal bone and marrow.

Röntgen Ray Studies: Bone age, 15 to 18 years. Chronological age, 15 years. Long bones and skull: Plain films of the skull showed a normal sella turcica. The pineal gland was not calcified. The anterior third of the calvarium was thickened but showed no evidence of striations (Fig. 1a). Films of the long bones, especially the tibia and fibula, ulna and radius showed the cortex to be very thin with the presence of both linear and cross striations (Fig. 2). The linear striations are a combination of lines of increased and decreased density. The cross striations are lines of increased density.

April, 1935. Tuberculin test, 1 : 10,000 negative; 1 : 1000 negative.

Gastric analysis showed no free HCl in the fasting specimen but showed 48° after 15 minutes with a total acid of 56° .

Vital staining showed fragmentation of the cells with marked motility of the red cells and fragments.

In February, 1938, the hemoglobin was 50% (Sahli); erythrocytes, 3,000,000; leukocytes, 7500. No nucleated red cells were seen.

The menarche was not established until the age of 16, following a course of endocrine therapy. She is now 5 feet 6 inches tall, weighs 115 pounds, and except for the pallor and icterus resembles any normal young adult in appearance. She has finished high school and now works steadily in a clerical position. She has had less than the average amount of minor respiratory or contagious infection.

The brother has had a more stormy course although he now appears to be better adjusted to his disease. The amount of activity compatible with a severe anemia in these cases has been of interest and is significant of the ability of the body to adjust itself to a chronic state of disease. The cardiac hypertrophy (Fig. 3) usual in this disease may be a compensatory factor.

CASE 2.—S. P., aged 17, was first seen in 1926 at the age of 4. His complaints were the same as his sister's, namely yellow color, weakness and

a mass in the abdomen. At the age of 1½ years he had eaten dirt and newspapers, but he does not fall into Caminopetros' classification of "Geophagists"^{2a} because he has a very definite Mongolian facies. This, however, is more striking in real life than in his photograph (Fig. 4).

He was well nourished but had the peculiar muddy icteric tint of his sister. There was a systolic murmur heard widely over the precordia. The spleen, which was similar in size to that of his sister, reached to the iliac crest and almost to the midline. The liver was not so large but was palpable in the epigastrium.

Laboratory Data. Hemoglobin, 20% (Sahli); erythrocytes, 1,992,000; leukocytes, 10,000; differential count: neutrophils, 39%; lymphocytes, 60%; myelocytes, 1%. There were 7 nucleated reds to every 100 white cells counted. The smear showed marked anisocytosis and poikilocytosis. Fragility test: Hemolysis began at 0.375 and was not complete at 0.025, the lowest dilution. The Wassermann test was negative. Bleeding time, 12 minutes; coagulation time, 5 minutes; blood Group IV (Moss). The urine was negative for bile but positive for urobilin.

In May, 1928, he developed an acute mastoiditis and was successfully operated upon after a transfusion of 250 cc. of his father's citrated blood.

Because at this time the children were classified as cases of familial hemolytic jaundice (although thought to be atypical because of their increased red cell resistance to hypotonic salt solutions), it was deemed wise to perform a splenectomy on the boy. He was chosen rather than the girl because of the more severe anemia, tendency to infections which are often fatal in this group, and his greater youth. Therefore, in July, 1928, a splenectomy was done following a transfusion of 500 cc. of his father's citrated blood. At operation, adhesions were found between the spleen and stomach and the tail of the pancreas. Unfortunately, the pathologic report and sections of the spleen are not available. Following operation showers of nucleated red cells were found in his peripheral blood and this has persisted to the present day. (Noted in other cases following splenectomy.) His hemoglobin was 65% on dismissal from the hospital.

In May, 1928, he was injured slightly in an automobile accident. Skull plates at this time showed thickening of the calvarium (Fig. 5a).

In June, 1932, he was hospitalized again for study and for the first time these two children were recognized as cases of Cooley's anemia. Laboratory data at that time: Hemoglobin, 50% (8.5 gm.); erythroblasts, 4,230,000; leukocytes, 12,000; differential neutrophils, 29%; eosinophils, 12%; basophils, 1%; lymphocytes, 26%; myelocytes, 19%; disintegrated cells, 13%. There were 9.6% nucleated red cells. Reticulocytes, 3.2%; platelets, 650,000; cholesterol, 95.7 mg. per 100 cc. plasma; calcium, 10.4 mg. per 100 cc. serum; inorganic phosphorus, 5.6 mg. per 100 cc. serum.

Roentgen Ray Studies. The skull was markedly thickened and showed the vertical type of striations, especially in the posterior two-thirds (Fig. 5b). The distal end of the left humerus and the proximal portion of the ulna and radius showed marked thinning of the cortex and a peculiar type of transverse and trabeculated striations (Fig. 6a). The pelvis, proximal ends of the femora and lumbar vertebrae also showed peculiar trabeculated striations together with a moderate amount of diffuse demineralization (Fig. 6b). These changes were also apparent in the ribs, clavicle and scapulae.

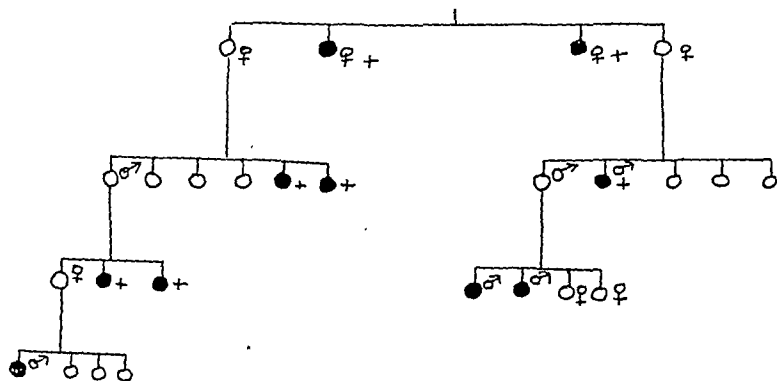
In March, 1935, the boy had a febrile period with temperatures ranging between 101° and 103° F. This gradually subsided but 1 week after onset his eyes and scalp became very swollen. There was a deep depression on the back of his scalp with a circle of edema around it the size of a doughnut. There was no edema elsewhere. He was hospitalized at once. Skull plates while showing changes even more marked than on the previous entry, failed to reveal anything to account for the peculiar distribution of the edema.

Serum protein studies were as follows: Albumen, 3.45%; globulin, 2.57%; total, 6.40%; ratio, 1.35. Hemoglobin, 21%; erythrocytes, 1,630,000; leukocytes, 15,500; color index, 0.6. He was transfused with his father's blood and showed the marked improvement that a transfusion always produced in him.

About this time severe headaches occurred and lasted for 2 or 3 years. Sinus examinations and refraction failed to reveal any cause for them and during the past year they have entirely disappeared. He is now in better health than at any time in his history. His last blood count is as follows: hemoglobin; 47% (8 gm.); erythrocytes, 3,440,000; leukocytes, 19,200; differential count: Neutrophils, 16%; eosinophils, 3%; lymphocytes, 79%; monocytes, 1%; nucleated red cells, 8%.

Family History. The parents, both of whom are healthy, were born in the Eastern Mediterranean area, the mother in Hora on the Sea of Marmora and the father on the Isle of Thassus. This region was originally Turkish but the grandparents were Greeks who had migrated there. They know of no other cases similar to this type of anemia among their relatives. The mother suffered from chlorosis as a child. The parents' blood counts have been checked during this study and were found to be normal.

Therapy. The therapy of these children has consisted of daily generous and constant doses of iron, in the form of the saccharated carbonate, ferrum reductum and ferric ammonium citrate, as well as cod-liver oil. Why they have lived longer than the usual allotted span of children suffering from this disease is not known; but it is possible that there are *formes frustes* which have not hitherto been recorded in the literature.



Key.—+ dead, ○ healthy or apparently healthy, ● afflicted with erythroblastic anemia.

FIG. 7.—Genealogic table showing transmission of erythroblastic anemia.
(From Caminopetros.)

Discussion. Caminopetros,^{2a} working in the Pasteur Institute of Athens, Greece, where he has studied 36 new cases to add to the 56 cases already published in the literature, has presented recently some findings regarding the relatives of these anemic patients and postulates a new theory as to its transmission. He reveals the missing link by studying several cases in different generations of the same family, one even passing through four traceable generations. In his series there were several families in which the disease occurred in two generations. It is evident from his genealogies, one of which is

here reproduced (Fig. 7), that the disease is transmitted according to the Mendelian law as a recessive characteristic.

Furthermore, Caminopetros^{2a} has shown by an extensive study that one of the salient features of the disease, *i. e.*, the increased resistance of the red blood cells to hypotonic salt solutions, occurs not only in the members of the family afflicted with the disease but also in the apparently healthy members of the family who are the carriers of it, thus helping to propagate it. This finding had never before been noted nor had the fact that the diseased child invariably belongs to the same blood group as the carrier parent. It has been predicted also that the healthy carrier would show characteristic changes in his bones, but we were unable to substantiate this in our study of these 2 cases.

If these findings regarding the transmission of the disease are proven to be constant on further study, they could be of enormous value in controlling the spread of erythroblastic anemia. In other words, neither those obviously afflicted nor the healthy appearing siblings of the patient who show increased resistance of their red blood cells should procreate. This may seem to be of rather theoretical significance because of the relative rareness of the disease. But, as Caminopetros^{2a} notes, it has been suggested that older civilizations have been decimated by this disease. Vogt and Diamond⁶ mention changes in the skeleton of the Mayans which are thought to correspond with those of erythroblastic anemia.

Caminopetros^{2a} subdivides the disease into three sub-groups: 1, The usual type with characteristic Mongolian features; 2, another type with radiologic changes in the skull but without the Mongolian features (these he labeled "geophagic anemia," or the anemia of dirt eaters); 3, a form with elongated erythroblasts suggestive of sickle cells but without true sickling.

Mongolian Facies. Searching the family trees of his cases brought out the surprising fact that often the grandparent of these so-called Greeks was a native Chinese who had migrated to Asia Minor. This might account for the "Mongolian eye" occasionally found in his families but not connected in any way with the disease. This is produced by a fold which arises from the depressed bridge of the nose, giving an oblique appearance to the eye. This Chinese eye is very obvious in the one member of our family (Anna P.) who does not show any stigma of the disease. It, therefore, might be thought of as a racial characteristic in this girl, although no Chinese ancestry could be elicited, perhaps because the parentage could not be traced back more than two generations. In those patients with changes in the bone, the facies is a part of the disease *per se* and not racial. Again, in an entirely unrelated disease, Mongolian idiocy, the facies is a part of the disease and is not hereditary. Unlike the changes in erythroblastic anemia, however, it is associated with a hypoplasia of the bone.^{2b}

Splenic and liver punctures were done routinely in Caminopetros' series. These show a more striking and characteristic picture than sections of the sternal marrow which usually proves to be normal, as in one of our cases (D. P.).

In view of Caminopetros'^{2a} statement regarding the Mendelian character of the red cell fragility this factor, as well as the blood grouping, was tested in the entire family. The results concur with his statement that healthy appearing siblings may present this stigma of the disease and are, therefore, potential carriers.

TABLE 1.—FRAGILITY TESTS OF FAMILY.

	<i>Hemolysis begins.</i>	<i>Hemolysis complete.</i>
Mother	0.40% NaCl	0.04% NaCl
Control	0.42% "	0.22% "
Father	0.38% "	0.08% "
Control	0.42% "	0.28% "
Sister As.	0.40% "	0.08% "
Control	0.42% "	0.28% "
Sister Anna	0.40% "	0.26% "
Control	0.42% "	0.28% "

Attention is called again to the fact that sister Anna, who has normal red cell resistance to hypotonic salt solutions and is therefore probably not a carrier, does have a very striking Chinese facies.

The blood groups of the 2 patients and the father fall among those commonly found in Caminopetros' series, namely Group IV. Roentgen rays of the long bones and skull of the parents did not reveal any abnormalities.

Summary. 1. Two cases of erythroblastic anemia are presented which have been followed over 12 years.

2. A review is presented of earlier theories regarding the etiology and transmission of erythroblastic anemia with particular reference to more recent work at the Pasteur Institute in Athens.

3. The result of studies there has led to the conclusion that erythroblastic anemia may be transmitted by healthy appearing relatives of those exhibiting the disease.

4. These carriers may be recognized by testing their blood for resistance of the red cells to hypotonic salt solutions. It is invariably increased.

5. This increased resistance is transmitted as a Mendelian recessive character.

The author is indebted to Dr. Alexander Petrilli, Roentgenologist to the Children's Hospital, for photographs of the Roentgen rays of these cases.
490 Post Street.

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MITOTIC LEUKOBLASTS IN THE PERIPHERAL BLOOD IN INFECTIOUS MONONUCLEOSIS.

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THE diagnostic import and the biologic significance of "pathologic" immature cell forms in the peripheral blood of patients are sources for entertaining consideration. The appearance of immature cell forms in the blood permits one to guess at what is taking place at the less accessible points of origin in the hematopoietic system—and one wonders what influences are responsible that these unicellular immatures or sports get away from home before they are mature enough to fend for themselves in the peripheral circulation—and one wonders what their fate may be.

Particularly, the appearance of actively dividing cells in the peripheral blood is thought stimulating both because of their rarity and because they suggest the uncontrolled behavior of the cells of malignant neoplasm. Examples of the amitotic division^{2,14} of leukoblasts are spectacular; the appearance of mitotic erythroblasts and leukoblasts is even more so.^{1-3,6,7a,b,9,11,13,15}

It is the purpose of this report to call attention to the occurrence of leukoblastic mitotic figures in the peripheral blood of patients during the active stage of infectious mononucleosis, and to infer from the complete recovery of such patients that the discovery of these cell forms, when considered in conjunction with other findings, is not of serious prognostic significance.

In a discussion of the cell forms of one of the author's cases of leukemia² during 1929, Foster M. Johns related a case of infectious mononucleosis with recovery in which he had noted mitotic leukoblasts. During 1931 the author displayed at the meeting of the American Medical Association a series of colored photomicrographs of the peripheral blood cell forms from John's case and 2 other cases of infectious mononucleosis. Cells containing two nuclei and cells showing mitotic division were represented in the 3 cases. Nyfeldt¹¹ has published probably the first and only plate showing mitosis in this condition; Heck⁸ states: "Immature lymphocytes and even mitosis have been described." So far as I am aware, no other mention has been made of the mitotic cell in infectious mononucleosis. If this is true, John's observation is the first.

The following remarks are based upon the study of 3 cases of infectious mononucleosis. It is unnecessary to record the cases in detail as they presented no unusual clinical features.

It would seem that the mitotic leukoblasts appear in the peripheral blood during the course of infectious mononucleosis near the

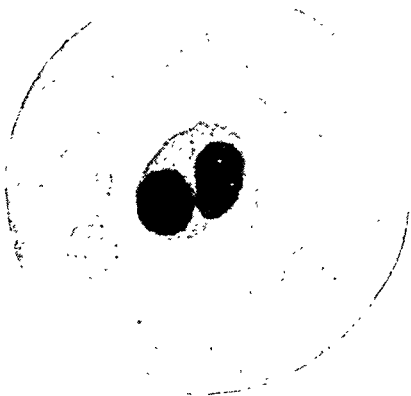


FIG. 1

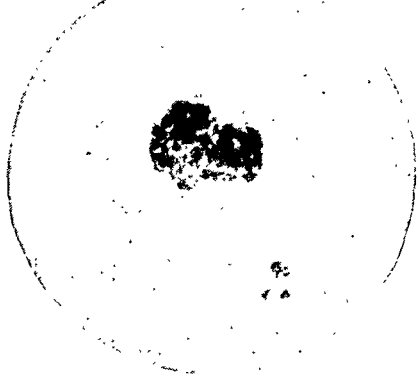


FIG. 2

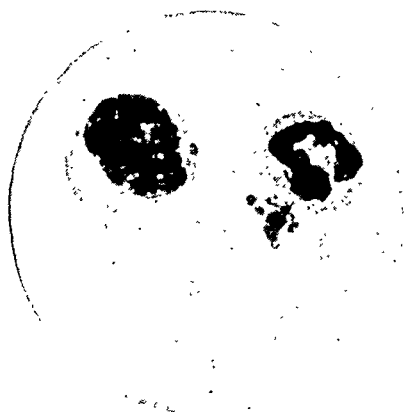


FIG. 3



FIG. 4

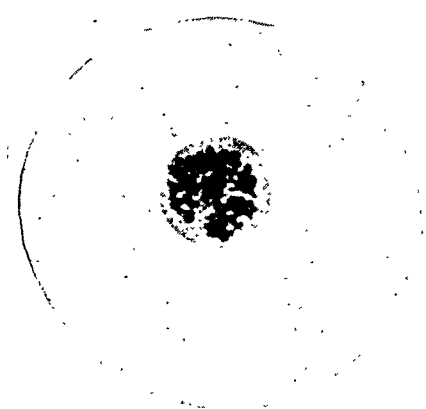


FIG. 5



FIG. 6

FIGS. 1 to 6.—Photomicrographs of peripheral blood from cases of infectious mononucleosis; these were made by Miss Stella Zimmer in the Photographic Department of the Medical School of the University of Syracuse through the courtesy of Dr. W. A. Groat. (About $\times 1100$.)

FIGS. 1 to 3.—Case 1, case of Foster M. Johns, a 20-year-old son of a physician; complete recovery. Fig. 1: cell with 2 nuclei; FIGS. 2 and 3: examples of mitosis.

FIGS. 4 and 5.—Case 2, female aged 9 years; had a rather prolonged mild course and exhibited slight secondary anemia. Complete recovery. Fig. 4: cell with 2 nuclei; Fig. 5: example of mitosis. Dr. W. A. Groat has furnished the interesting comment on this cell after his examination of the stained blood smear: "This cell undergoing mitotic division at an early stage shows the full, $2n$, number of chromosomes, or at least of the order of 48 . The others are so early in the prophase that while they seem to be of the $2n$ or normal type they have not separated or arranged themselves with sufficient regularity to make accurate count possible. Since none of these cells had progressed beyond late prophase, there is no spindle formation and therefore no angles can be measured."

FIG. 6.—Case 3, probably a very early arrangement of the nuclear chromatin into coarse masses preparatory to mitotic division.

peak rise of the leukocyte count. As the number of such mitotic cells is small, they are best discovered by careful complete low-power examination with rather bright illumination of a number of polychrome-stained blood smears. In contrast to the leukemic blood picture, in which all stages of mitotic division may be found, I have discovered only the early stages of mitosis in infectious mononucleosis; in these stages the chromatin configurations are sharper and cleaner-cut than those seen in the early stages of mitosis in leukemic bloods.

From the practical standpoint, it is important to call attention to these mitotic leukoblasts. The course of infectious mononucleosis often presents a problem of difficult differential diagnosis and hence prognosis in both the clinical picture and the blood picture. In those cases with a marked resemblance to leukemia, with a negative test for heterophile antibody, slight anemia, and the discovery of mitotic leukoblasts, an unnecessarily dark outlook could be taken of a relatively benign condition. The test of time makes the final diagnosis, but it is most difficult to wait.

In general, one may say that the blood picture of infectious mononucleosis appears rather characteristic to the initiate (although one must exercise caution to remain in the initiate class). Classic descriptions⁴ call attention to the vacuolization of the cytoplasm of the immature cells and more or less characteristic fenestration of the chromatin network of the nucleus of the immature cell. Blood platelets are present in normal numbers. There is little or no occurrence of a progressive decrease in hemoglobin and red blood cell numbers, and *no* appearance of nucleated red blood cells (while leukemia produces a progressive anemia with the peripheral appearance of erythroblasts). Great help is derived from a positive heterophile antibody test or cell agglutinin adsorption test.^{5,10,12} The clinical course may be of little diagnostic value until improvement and eventual recovery occur. The story of this morbid entity has been so completely described that it requires no mention here.^{4,5,8,10-12}

Summary. In infectious mononucleosis, mitotic leukoblasts and other unusual cell forms may appear in the peripheral blood near the peak rise of the leukocyte count. The occurrence of such immature and unusual cell forms is emphasized in order that confusion may be avoided in the diagnosis of this relatively benign illness which often resembles acute leukemia in many respects.

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THE PROGNOSTIC SIGNIFICANCE OF EOSINOPHILS IN THE BLOOD IN PNEUMONIA.

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THE differential leukocyte count in pneumonia, as well as in other acute infections, has been the subject of study for many years, usually along lines such as those proposed by Arneth and Schilling. From such studies, based on daily or even more frequent counts, it has been claimed that a graph of the patient's progress could be charted.

The time required in making such examinations, and the individual variation in recognition of the stages of maturity of the neutrophils (and therefore individual error) have practically precluded the use of such tests as routine studies in many clinics. A simpler and possibly more exact test might be a study of the presence or absence of any one type of cell, and the correlation of this finding with the clinical state of the patient ill with pneumonia. Accordingly, from observations on the blood smears from cases of pneumonia which form the basis of this paper, we have limited ourselves to a study of the eosinophils, especially their relationship to prognosis.

Previous studies have been made on the relationship of eosinophils to pneumonia and other acute infections. Hinkleman⁶ and others^{2,10} reported that eosinophils are absent from the blood in severe acute infections, and Eisenberg and Nemens⁴ claimed that the eosinophils disappear with the onset of acute infections. Other reports^{3,9} substantiate these findings. Becker¹ claimed that the absence of eosinophils in pneumonia was an unfavorable sign, and stated that he had never found eosinophils in fatal cases. Whitby and Britton¹¹ agreed with this finding in general: "In cases of pyogenic infection, prolonged absence of eosinophils is associated with a bad prognosis." It has also been noted^{7,11} that in convalescence from acute infections the eosinophils reappear in the blood and in many cases exceed the normal numbers. Kohlman⁷ and Rogatz¹⁰ published studies of the Schilling index in pneumonia and claimed that "the reappearance of eosinophils was a favorable sign,

often confirming recovery." Gradwohl⁵ states that the return of eosinophils in acute infections, particularly pneumonia, is "the dawn of convalescence."

In the pneumonia service at Mercy Hospital daily leukocyte counts are made on all cases during the febrile stage, and it is from 180 of these adult cases that the data for this report has been collected. Of the number, 163 had received the quinine derivative, hydroxyethylapocupreine,⁸ while 17 had received only the usual symptomatic treatment. A few observations have been made on patients treated with antipneumococcic horse serum, but the number is so small that these have been excluded from the series. A similar study, however, on this serum group might well be instructive.

Method. Smears were examined daily until the leukocyte count had returned to normal and the patient had recovered clinically. A total of 1046 smears were examined (average, 5.8 smears per patient, with a range of 1 to 33). Wright's stain was used for all smears, and the smears were examined under the high dry lens. It is necessary to use the oil immersion only in corroborating the finding of eosinophils. To minimize the factor of personal error, all staining and examinations were done by one person. In 40 cases, 200 leukocytes were counted on each smear; in the remaining 140 cases, from 500 to 1000 cells were counted. In those smears showing eosinophils, the cells were invariably noted before 400 cells were counted.

Since the studies included in this paper were completed, we have been using the differential counting fluid suggested by Hinkleman.^{6a} This fluid is used instead of the ordinary diluting fluid. It clearly stains the eosinophils, thus making the recognition of these cells possible while the total leukocyte count is being done. In the comparatively small experience we have had with this method, the results justify its further use.

Of the 180 cases, 120 recovered and 60 died. In the recoveries, the average number of daily blood smear examinations was 6.7, ranging from 1 to 17. The eosinophils were entirely absent from the blood stream for an average of 5.8 days after onset in 105 cases that recovered under treatment with hydroxyethylapocupreine (range 1 to 13 days). The absence of eosinophils lasted for an average of 8.8 days in 15 untreated recoveries (range 5 to 18 days).

Six of the 120 recoveries showed eosinophils in the blood on admission. These were all early cases of mild pneumonia, recovering within 24 to 36 hours after institution of treatment with hydroxyethylapocupreine. In 42 cases eosinophils were present from 1 to 5 days before any clinical evidence of recovery could be noted. In 55 cases the appearance of eosinophils and definite signs of improvement in the patient occurred at the same time, while in 23 cases recovery preceded the appearance of eosinophils by 1 to 3 days.

At the time of appearance of eosinophils, the total leukocyte count in the individual cases ranged from 4400 to 32,000, with an average of 12,700. Eosinophilia was a frequent but not a constant finding, the normal range of eosinophils being taken as 75 to 240 per c.mm.

(1 to 4%). In the recoveries in our series, 58 cases (47) had an eosinophilia above 240 per c.mm. at some time during convalescence. The highest number of eosinophils in the recoveries ranged from 24 to 1284 per c.mm. (average, 310).

Of the 127 cases who showed eosinophils at any time during hospitalization, only 7 (3.8%) died. It is of interest to note the cause of death in these cases:

C. B.—Pneumococcus Type II pneumonia, later developing pneumococcus Type II endocarditis; died 16 days after onset of pneumonia.

G. Q.—Died of uncomplicated pneumococcus Type III pneumonia with bacteremia, but eosinophils were present only once shortly after blood transfusion had been given.

L. S.—A Type II pneumonia with bacteremia. The eosinophils appeared on the eighth day of disease, accompanied by the clinical appearance of crisis, and a negative blood culture. The patient then developed delirium tremens and died on the ninth day of disease.

R. Z.—An influenzal bronchopneumonia (bilateral, pneumococcus Type II with no bacteremia). Eosinophils were present on the third day only, and on that day there was a definite clinical improvement. Acute influenzal meningo-encephalitis developed on the fourth day of disease and the patient died at the end of the seventh day. Diagnosis of encephalitis was confirmed at autopsy.

J. O.—Died of *Staphylococcus aureus* empyema 36 days after the onset of pneumonia. Autopsy showed resolution and organization of the pneumonic process.

M. C.—Died on the fifth day of disease, after 2 days of wild delirium tremens. There had been clinical improvement on the third day, the only time eosinophils were found in the blood.

P. R.—Died on the thirteenth day of disease, of pneumococcic endocarditis and meningitis, proved at autopsy. The lungs showed resolution and organization of the pneumonia. Eosinophils were present on the eighth day only.

Six of these 7 cases (excluding the one in whose blood eosinophils were found only after transfusion) showed some clinical improvement when the transitory presence of eosinophils occurred. And in all 6 the eosinophils disappeared when the complications developed.

Of the remaining 53 deaths, eosinophils were absent from the blood during the entire course of the disease. These patients had from 1 to 11 daily smears examined (average, 3.1). Of these, 44 died of uncomplicated pneumonia. The remaining 9 developed fatal complications which need not be detailed here.

Eisenberg and Nemens⁴ reported that they had never seen eosinophils in the blood of pneumonia patients prior to the development of empyema. Such has not been our finding. Our cases developing empyema have been few in number, but most of them showed eosinophils early during resolution of the pneumonia, and preceding development of the empyema. The eosinophils then tended to disappear as the empyema developed. Indeed, one of the fatal cases developed empyema after a temporary reappearance of eosinophils.

It seems evident that the primary depression of eosinophils is due to the infection itself. We have no hypotheses to offer regarding either the reappearance of eosinophils in recovering cases, or the eosinophilia which occurs during convalescence. We have not noticed any association in the use of hydroxyethylapocupreine with either the continued absence of eosinophils or their reappearance, other than the fact that patients receiving hydroxyethylapocupreine showed eosinophils earlier than the untreated ones. This was apparently associated with their earlier clinical recovery.

Conclusions. 1. Eosinophils are entirely absent from the blood early in the disease in severe pneumonia, but may be present early in milder cases.

2. The appearance of eosinophils in the blood of pneumonia patients treated with hydroxyethylapocupreine or not specifically treated is an index of recovery, and may precede clinical improvement by one to several days.

3. Eosinophils were not found in the blood of patients dying of uncomplicated pneumonia.

4. The reappearance of eosinophils during the course of pneumonia, while in itself a favorable sign, does not exclude the possibility of a serious and even fatal complication developing later.

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AN EVALUATION OF THE PHENOLPHTHALEIN TEST OF WOLDMAN.

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In a recent preliminary report Woldman⁴ describes a simple test for the detection of a lesion in the gastro-intestinal tract. The test is based upon the qualitative determination of phenolphthalein

in the urine after the administration of 0.1 gm. in an alcohol solution by mouth. In a series of 112 cases Woldman found the error to be less than 3%. Our experience with 115 hospital patients is reported herewith to enable further evaluation of the test as a diagnostic procedure.

The chemical and pharmacologic characteristics of phenolphthalein have been described very well by Vamossy³ and Fantus.¹ Phenolphthalein is widely used as a mild laxative. In the bowel, it is dissolved by the bile and alkaline secretions; however, very little is absorbed, almost 90% appearing unchanged in the feces.² It has been detected in the urine in some instances, 48 to 72 hours after ingestion.⁴ Phenolphthalein produces a pink or red color in alkaline solutions, and its presence in extremely high dilutions is shown distinctly by the addition of alkali to the urine.

Method. The technique of examination used by us was essentially that recommended by Woldman. One gram of white phenolphthalein was dissolved in 100 cc. of 95% alcohol. The dose administered was 10 cc. of this solution or 0.1 gm. of phenolphthalein. The procedure was as follows: The patient was allowed no food or water after midnight. The following morning at 7, a control urine specimen was obtained. Ten cc. of the phenolphthalein solution, diluted to 30 cc. by the addition of water, was then administered. The patient was instructed to drink the medication through a straw to avoid contact of the solution with possible ulcerations in the mouth. Special precautions were taken also to prevent contact of the medication with the patient's hands, thus obviating the occurrence of false positive reactions which might result from contact of the drug on the fingers with the urine specimens. The patient was not allowed to eat or drink for 1 hour after taking the medication; the previous regimen then was resumed. Urine specimens were obtained at 7 A. M. (control) and then 1, 2, 4, 6, and 8 hours later. We noted, however, that in no instance was the 6 or 8 hour examination positive without a corresponding result in earlier urine specimens, indicating that prolongation of the period of testing beyond 4 hours does not increase the diagnostic efficiency of the test. The specimens were examined fairly promptly as advised by Woldman. In many cases, as will be noted later, the test was repeated after a minimum interval of 72 hours. A portion of each urine specimen was poured into two containers, one to be used for comparison of color with the other portion, to which 10% sodium hydroxide was added. The sodium hydroxide was added with a dropper until no more change in color took place.

Clinical Study. The test was performed on 44 patients with gastro-intestinal disease; 30 of these had duodenal ulcers, 27 of which were considered to be active clinically and 3 inactive. The test was positive in 15 of the active cases. Eight of the 12 negative-reacting patients were examined twice with identical results. Negative reactions occurred in 2 of the 3 patients with inactive duodenal ulcers. One patient with a gastric ulcer gave a negative test when the ulcer presumably was healed, whereas the positive reaction appeared when the ulcer recurred, a definite crater being found roentgenologically and occult blood being present in the stools. Three patients, each giving positive test, were not completely diagnosed at the time

of this report. In these 3 cases the validity of the positive test has neither been proved nor disproved. The remaining positive results in the group with organic gastro-intestinal tract disease were obtained in patients with atrophic gastritis, carcinoma of the stomach, chronic diverticulitis of the colon, miliary tuberculosis and carcinomatosis of the peritoneum. It will be noted (Table 1) that the test was negative in 12 of the cases of active duodenal ulcer and positive in 1 of the 3 inactive ulcers. Negative reactions were encountered in this group in 17 cases when positive reactions presumably were to have been expected, giving a "negative" error of approximately 38%.

TABLE 1.—RESULTS OF PHENOLPHTHALEIN TEST IN PATIENTS WITH ORGANIC GASTRO-INTESTINAL DISEASE (44 CASES).

Diagnosis.	Cases.	Result.	
		Positive.	Negative.
Duodenal ulcer (clinically active)	27	15	12
		(8 patients tested twice)	
Duodenal ulcer (clinically inactive)	3	1	2
Atrophic gastritis	3	3	
		(1 patient tested twice)	
Carcinoma of stomach	1	1	
Chronic diverticulitis of colon with benign papil- loma of sigmoid	1	1	
Gastric ulcer	2	1	2
		(1 patient tested twice)	
Chronic bacillary dysentery	1	..	1
Miliary tuberculosis with tuberculosis of small bowel	1	1	
Carcinomatosis of peritoneum (primary site un- known—Roentgen rays negative)	1	1	
Inflammatory stricture of rectosigmoid, benign polyps of rectum (biopsy)	1	..	1
Unclassified:	3	1	
1. Hematemesis with gross blood in stools			
2. Secondary anemia; blood in stools	1	
3. Neoplastic involvement of sternum; gastric complaints vague	1	
Totals	44	27	18

The phenolphthalein test, to be considered a reliable indicator of the presence of gastro-intestinal lesions, should be positive only in those cases with gastro-intestinal disease. To test this hypothesis, a group of 71 patients (Table 2), thought clinically to have no organic gastro-intestinal disease, were examined. The absence of a lesion was confirmed in most instances by Roentgen and laboratory studies, and in several patients at necropsy. The test was negative in 38 cases and positive in 33 (repeated twice in 14 of this latter group with identical findings). One patient with an unexplained low grade fever gave positive results in 4 tests repeated at intervals of 4, 16, and 24 days. The test was positive in 6 of the 7 cases of pulmonary tuberculosis; in the 6 positives two examinations were made. It is, of course, possible that these patients may have tuberculous involvement of the bowel, although in each case the

clinical findings did not indicate this possibility. Positive reactions were obtained in 11 of the 14 patients with various chest conditions, including tuberculosis. The explanation of this finding is not evident. Positive tests were obtained also in patients with diabetes, hypertensive heart disease, neurodermatitis, infectious arthritis, and sacro-iliac disease, among others. The "positive" error in this group was approximately 46%.

TABLE 2.—RESULTS OF PHENOLPHTHALEIN TEST IN PATIENTS WITHOUT ORGANIC GASTRO-INTESTINAL DISEASE (71 CASES).

Diagnosis.	Cases.	Result.	
		Positive.	Negative.
Normal males	2	..	2
Diabetes mellitus	9	2	7
Pernicious anemia	3	3	
Luetic heart disease	2	1	1
Hypertensive heart disease	7	3	4
Hypertension—diabetes	2	1	1
Arteriosclerotic heart disease	1	..	1
Auricular fibrillation	1	1	
Vasomotor instability	1	..	1
Obesity—postencephalitic	1	..	1
Thyrotoxicosis	1	..	1
Acromegaly	1	..	1
Lues with splenomegaly	1	1	
C. N. S. lues—cirrhosis of liver	1	..	1
Miliary tuberculosis (necropsy)	1	1	
Lupus erythematosus	1	..	1
Pulmonary tuberculosis	7	6	1
Bronchiogenic carcinoma of lung	2	2	
Sinusitis with bronchitis	2	1	1
Bronchopneumonia	1	..	1
Bronchial asthma	1	1	
Pleuritis (rheumatic or tuberculous)	1	1	
Psychiatric conditions	5	..	5
Neurodermatitis	1	1	
Functional bowel distress	2	2	
Torticollis	1	..	1
Postdiphtheritic pharyngeal paralysis	1	1	
Cellulitis of forearm	1	..	1
Unexplained fever (4 tests)	1	1	
Infectious arthritis	1	1	
Osteo-arthritis	1	..	1
Infectious mass retrocecal region	1	1	
Streptococcus sore throat	1	..	1
Cholecystitis—cholelithiasis	1	..	1
Bilateral hydronephrosis	1	..	1
Subacute nephritis	1	..	1
Sacro-iliac disease	1	1	
Paget's disease (skull and pelvis)	1	1	
Traumatic injury to back	1	..	1
Totals	71	33	38

It is interesting to note that positive reactions were obtained in all of the cases of pernicious anemia and all of those with atrophic gastritis without anemia. The question arises as to whether the phenolphthalein was absorbed through the atrophic gastric mucosa or through the intestinal mucosa, and whether the atrophic gastritis

is accompanied by or has any relationship to similar changes in the intestine which may affect the absorption of phenolphthalein.

Summary and Conclusions. 1. The phenolphthalein test, as described by Woldman, has been performed, with minor additions, on 115 patients; 44 with organic gastro-intestinal disease and 71 without a demonstrable gastro-intestinal lesion.

2. The "negative" error in patients with gastro-intestinal disease was approximately 38%, while the "positive" error in those patients clinically without a gastro-intestinal lesion was about 46%.

3. The phenolphthalein test cannot be relied on to prove or disprove the presence of a lesion in the mucous membrane of the gastro-intestinal tract.

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A "NUMERAL TEST" IN TRANSVERSE LESIONS OF THE SPINAL CORD.

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IN the determination of the presence of a spinal cord lesion as well as of its level, the examination of the sensibility plays an important and often a decisive rôle. This examination often enables us to determine more accurately than by any other clinical examination the level of a lesion in the spinal cord. It is chiefly in cases of compression of the spinal cord that we need exact determination of the level of involvement.

The question arises as to which of the numerous efferent and afferent tracts of the spinal cord suffer first in a diffuse compression of the cord. When such a transverse lesion exists, the afferent tracts in the posterior columns in all probability suffer first and most severely. This is due to the fact that the posterior columns, as Brouwer has shown, are phylogenetically comparatively young structures. Foerster^{3a} has observed numerous cases of marked compression in which, of the ascending afferent tracts, only the posterior columns were affected. In these cases the simple sensory qualities such as sensibility to touch, pressure, pain and temperature were preserved, and only the qualities specifically of the posterior columns were damaged. In all lesions on the posterior aspect of the spinal cord in which the posterior columns are immediately

affected—for example in posteriorly located tumor—the posterior columns of course suffer even more, and are affected very early. At all events, it may be accepted with some degree of certainty that in a compression of the spinal cord, the posterior columns apparently suffer earlier and more greatly than the anterolateral columns.

This early and predominant affection of the posterior columns, both in diffuse lesions of the spinal cord and in lesions on its posterior surface, renders it especially desirable to have a method which permits exact localization of a level at which there may be an interruption or damage in the conductivity of the posterior columns.

As we know, the posterior columns conduct sensibility to touch, pressure, posture and vibration, and also the space qualities of the touch sensibility.

For determination of the presence and level of an affection of the posterior columns, examination of the sensibility to touch and pressure is not appropriate because these sensory qualities are conducted through other spinal tracts also (the anterolateral columns). For technical reasons, examination of the vibratory and postural sensibility cannot yield the required information particularly with regard to the exact segment involved, especially in the area of the trunk. The space qualities of the touch sensibility comprise: 1, sense of localization; 2, two-point discrimination; and, 3, recognition by feeling of forms (*e. g.*, numerals) traced on the skin. If the space-sense of the skin is damaged by a lesion of the posterior columns, the sense of localization is markedly impaired and the patient makes such mistakes as ascribing a touch on a toe or finger to the wrong digit. The ability of the patient to recognize stimuli separated in location is markedly impaired. Two separated points may be recognized as such only when they are at a distance of 15 to 20 cm. apart. Disturbance of the space qualities of touch sensibility in a patient with a lesion in the posterior columns manifests itself further in that the patient is unable to recognize by feeling the direction and length of lines drawn on his skin. But the most striking disturbance is evidenced by the inability of the patient to recognize by feeling numerals traced on his skin.

The purpose of this article is solely to stress, from our experience of many years, the highly practical value of this much-neglected test of examination of superficial sensibility. While many of the leading textbooks on neurologic diagnosis, or on neurology, do not mention it at all, we find it referred to in the 7th edition of Monrad-Krohn's⁵ work (but not in the 6th), in Cadwalader's¹ book, and in a discussion by Fay². Monrad-Krohn speaks of "writing figures on the surface of the patient's skin," but when numerals are written this test is more easily performed and gives more reliable results.

This method, as far as we know devised by Foerster,^{3b} is very simple, is not tedious for either doctor or patient, and does not take much time; it requires, of course, the coöperation of the patient.

With the patient lying down with his eyes closed, the examiner traces on the patient's skin with a pointed but not sharp instrument (a nail, the butt of a percussion hammer, or a wooden stick) the following numerals: 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9. The patient is asked to state immediately what figure has been written. It is advisable to write the numerals parallel to the body axis and on all portions of the body, especially the trunk; and to determine the line below which the figures are not recognizable and above which they are recognizable. It is amazing how easily even less intelligent patients can recognize numerals, though small in size, and how sharply defined the line may be between the area in which the numerals are recognizable and that in which they are not.

Such a line corresponds exactly to the level of a transverse lesion of the spinal cord, and gives evidence of such a lesion earlier and more exactly than any other method. Foerster^{3b} reports cases of intramedullary tumors of which the only signs were spastic paraplegia and the inability to recognize, up to the involved level, numerals written on the skin. Sensibility to touch, pressure, pain and temperature were normal throughout. In many cases of my own, especially in instances of extra-medullary tumor and even more so in cases of extradural tumor, I have found this method to be more reliable than any other test for diagnosis of a compression of the spinal cord and for determination of its level. In a recently observed patient of Dr. H. C. Naffziger (case of compression of the thoracic spinal cord with paraplegia in flexion and complete subarachnoidal block), the numeral test revealed complete inability on the part of the patient to recognize numerals written on the skin below the level involved. Since other sensibilities were much less markedly affected, it was assumed that the lesion probably lay on the dorsal surface of the spinal cord. At operation, Dr. Naffziger found a large hemangioma on the dorsal surface of the spinal cord.

If there is a contradiction between the results obtained by this test and the results obtained by testing other sensibilities (touch, pain and temperature), it is usually when the numeral test indicates a lesion situated higher than the test of other sensory qualities indicates. In these cases the numeral test should be given the preference. The explanation of this is as follows: The anterolateral columns which conduct sensibility to touch, pain and temperature are arranged in such a manner that the innermost layers conduct the sensibility of the upper segments. In cases of compression of the spinal column, these innermost layers may be spared; therefore the upper areas below the lesion of the spinal column may show normal sensibility to touch, pain, and temperature, and the anesthesia for these qualities may begin much lower. In these cases the numeral test may reveal the actual level of a compression lying higher up; this is because the posterior columns have lower resistance and their whole area suffers from pressure.

The numeral test indicates a lesion of the posterior columns and of these only. This is best seen in patients with syringomyelia or gliosis spinalis. In these patients I have found on several occasions that numerals written on the skin of the affected area, that was completely anesthetic to pain and temperature, were very easily recognized, thus indicating that the posterior columns were intact.

This simple test should be familiar to every neurologist and physician. Knowledge of this test and of other simple clinical methods of detection of transverse lesions of the spinal cord, as, for instance, that recently described by Kerr,⁴ will certainly contribute in some cases to early detection of spinal cord lesions and may help to save some patients from the necessity of undergoing a myelographic procedure.

Summary. A normal individual can easily recognize by his sense of touch different numerals written on his skin. A segmental disturbance of this ability indicates the presence of a lesion of the posterior columns. Very early and reliable determination of the presence and level of a transverse lesion of the spinal cord can be made by this test.

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THE EFFECT OF ALTERATIONS IN THE METABOLIC RATE ON THE ACTION OF INSULIN.

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It is well known that a reduction in the apparent effectiveness of insulin follows the onset of infection and fever in patients with diabetes. Duncan, Fetter and Durkin⁵ believed, on the basis of clinical observations, that this was due to increases in the total metabolism. The present study was undertaken to further clarify this problem. Wien^{1,2,6} produced fever in rabbits by injecting killed *Bacillus coli communis*, and in this manner almost completely abolished the effect of insulin on the blood sugar concentration. The clinical studies presented here do not confirm Wien's interpreta-

tions, though results of experiments on animals, particularly on rabbits, cannot always be applied to man without modification.

Rabinowitch^{8a,b} studied the effect of a test dose of insulin on the blood sugar of diabetic patients with infections, with and without fever, and concluded that it was the infection and toxemia, *not the fever*, that reduced the effectiveness of the insulin. He based his conclusions on the blood sugar values found during the 3 or 4 hours which followed the injection of insulin, but it will be shown that more significant changes take place later.

Methods Employed. We have attempted to determine the effect of alterations in metabolism, without toxemia or infections, on the effectiveness of insulin. We increased the metabolism of normal persons and diabetic patients (a) by artificial fever, produced by giving typhoid vaccine intravenously and by using a Kettering hypertherm, and (b) by the oral administration of one dose of sodium dinitrophenol. The blood sugar concentration curve obtained after a test dose of insulin hydrochloride under these conditions is contrasted with the control curve obtained when the same amount of insulin was given but with no attempt to elevate the metabolism. The experiments were so planned that fever was present and the metabolism was raised during the test period. The time relationship between the onset of fever and the altered effectiveness of insulin is being investigated.

All subjects were kept in the hospital and given a constant diet for at least a week before and during the whole period of observation. In the case of diabetic patients, the insulin was stopped for 2 days before the special studies were begun, in order that there should be a fasting hyperglycemia on the day of the test.

The amount of insulin was not calculated entirely according to body weight, but for each patient a dose was given which was thought to be sufficient to produce a considerable reduction in the blood sugar level, without actually producing symptoms of hypoglycemia, as in the latter case, the secretion of epinephrin might affect the blood sugar values.

To obtain the control curve the fasting blood sugar was taken at 8 A.M. and immediately the insulin was injected subcutaneously, and 10 gm. of carbohydrate, in the form of fruit juice, were given by mouth. Subsequently, at 2-hour intervals, blood sugar estimations were made, each being followed by the administration of 10 gm. of carbohydrate. Apart from this, no food was given until the end of the experiment. Observations were continued until the blood sugar had regained its original level.

All sugar estimations were made on venous blood, using Benedict's¹ modification of the macromethod of Folin and Wu.

Artificial Fever Studies. Mixed typhoid vaccine was given intravenously 4 to 6 hours before observations were begun, in a dose sufficient to produce a rise of temperature (101° to 103° F.) during the experiment. At 8 A.M. the insulin was given, and blood sugar estimations were made at 2-hour intervals as already described. When the hypertherm was used, the patient was placed in the machine soon after the insulin had been injected, and similar observations were made during the period of fever. The curves obtained were compared with the controls obtained under identical conditions, but without fever.

Dinitrophenol Studies. It is known that an increase in metabolism of 30 to 50% occurs within an hour of the oral administration of 5 grains of dinitrophenol. This is maintained for 24 hours and normal metabolism is restored in from 3 to 14 days (Simkins¹⁰). In our study, sodium dinitrophenol (5 grains) was given by mouth in a single dose at 6 A.M. on the day

of the experiment. At 8 A.M. the same amount of insulin as was used in the control was given and blood sugar values were obtained and 10 gm. of carbohydrate were given at 2-hour intervals as already outlined.

The effectiveness of a given dose of insulin may be judged by the extent of the depression of the blood sugar below its fasting level and by the time taken for the blood sugar to return to this level. These values may be compared with the controls and alterations in the effectiveness can thus be determined.

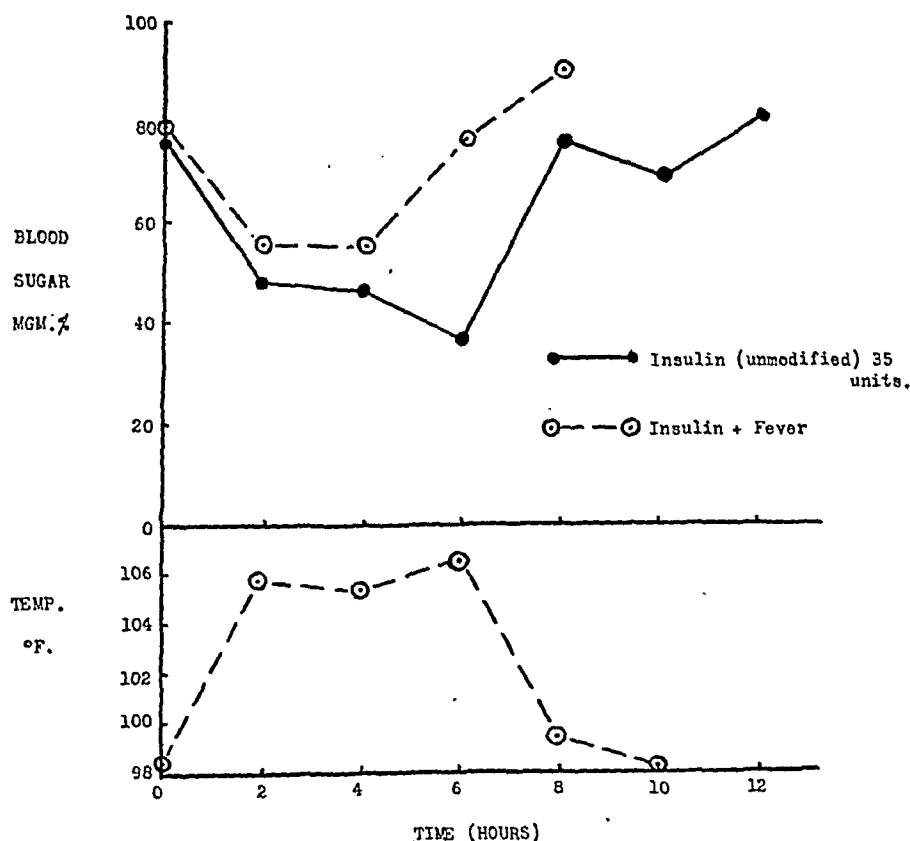


FIG. 1.

Results. Ten patients were given artificial fever, 3 of them having diabetes. There was little difference between the fasting blood sugar of the controls and the experiments; but, of the 7 non-diabetics, 6 showed a greater initial fall in the blood sugar level with fever than without. Five of the 7 showed a 20 to 50% reduction in the duration of insulin action, and in the remaining 2 there was little change. All 3 diabetics showed a shortening of the period of insulin action, and in 2 the depression of the blood sugar was less. Thus, for the whole group the most striking effect produced by fever was not a smaller fall of the blood sugar level but a shortened duration

of insulin action. Typical blood sugar curves obtained with normal and diabetic subjects are shown in Figures 1, 2 and 3.

Four patients were given dinitrophenol, and in all there was a definite shortening of the period of insulin activity (from 17 to 33%). Two cases showed a greater fall in blood sugar and in 2 there was no change in this respect (Fig. 4).

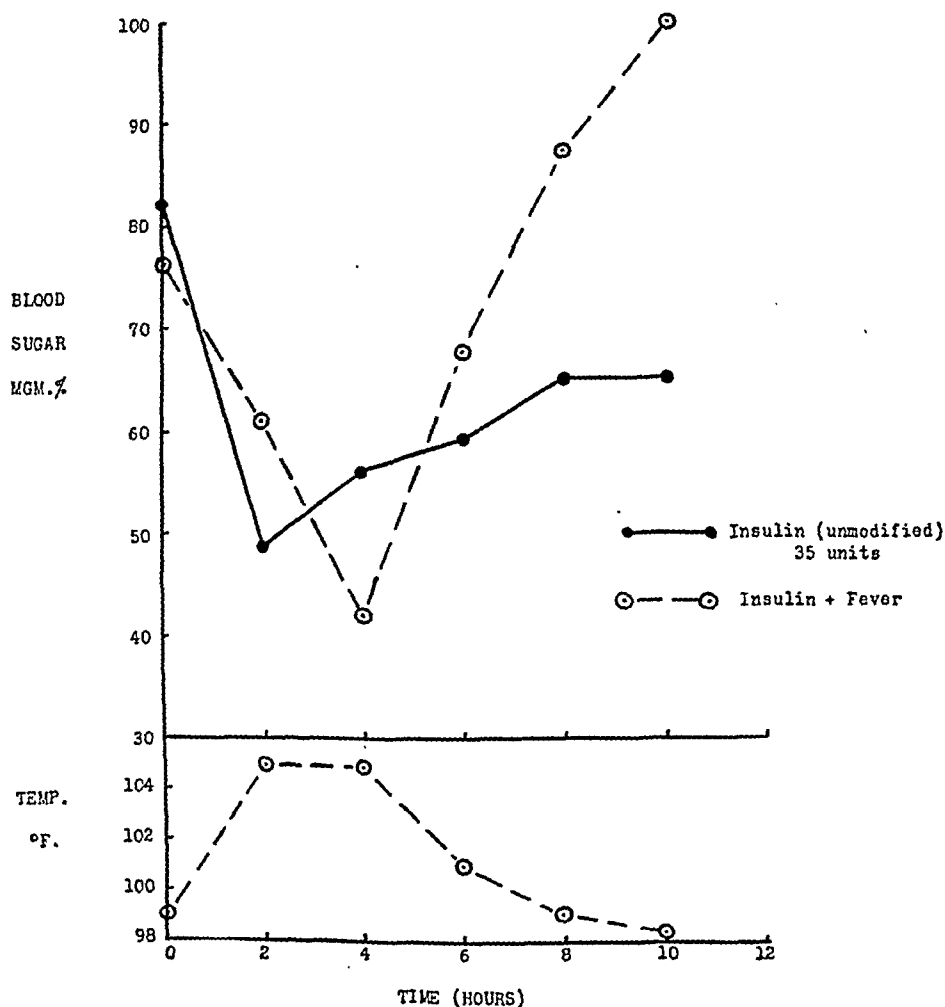


FIG. 2.

Figs. 1 and 2.—Blood sugar values obtained in 2 normal subjects after the injection of 35 units of unmodified insulin, with and without fever show the shortened duration of action of insulin during fever, with little change in the degree of depression of the blood sugar below the fasting level. The fever, in both subjects, was produced by the hypertherm.

Discussion. The basal metabolism during artificial fever has been studied by Schafer-Fingerle,⁹ who found that an increased tissue oxidation accompanies the fever and may occur independently of it. Similarly, with sodium dinitrophenol, the metabolic stimulation is

accompanied by an increased tissue oxidation, mainly at the expense of fat (Simkins¹⁰), although there is usually no rise in temperature after its administration. The effect of both of these factors—fever and dinitrophenol administration—on the blood sugar curves follow-

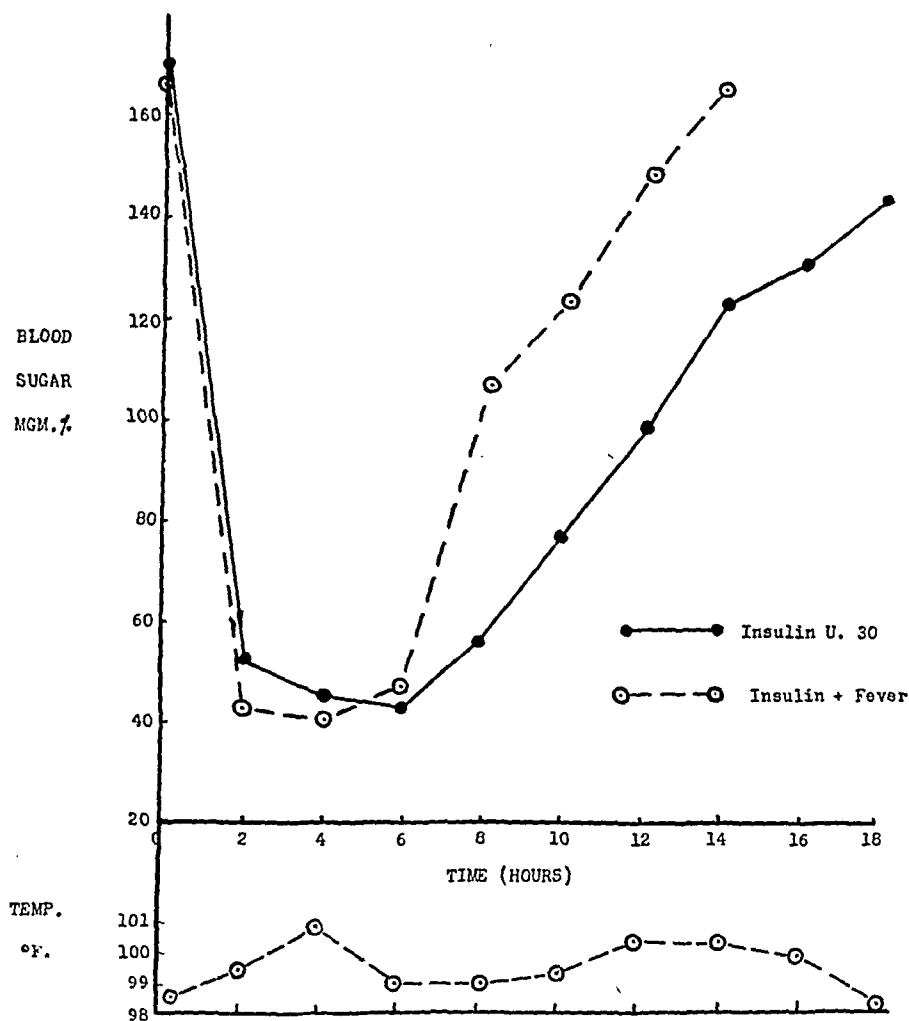


FIG. 3.—Blood sugar values in a diabetic subject, after 30 units of unmodified insulin were given subcutaneously, are contrasted with those after the same amount of insulin during a period of artificial fever produced by typhoid vaccine. In the former, the fasting blood sugar was not regained in 18 hours, while in the latter it was regained in 14 hours. Note that the actual fall in the blood sugar concentration in each case was almost identical.

ing the injection of insulin is the same—namely, a shortening of the period of insulin activity, and it is reasonable to suppose that this is due to increased peripheral utilization of insulin by the tissues during increased metabolic activity. It would seem that increases in the total metabolism shorten the period over which insulin is

active. However, we realize that this is not apparent during physical exercise when much glucose is oxidized.

The effects of the increased metabolism in hyperthyroidism, and those produced experimentally by the oral administration of thyroid substance have also been, and are being, studied, but the results are difficult to assess because of the changes in liver glycogen and body weight which occur. On the whole, they support the observations of deWesselow and Griffiths,³ who found that insulin-resistant cases of hyperthyroidism became normally insulin sensitive after the

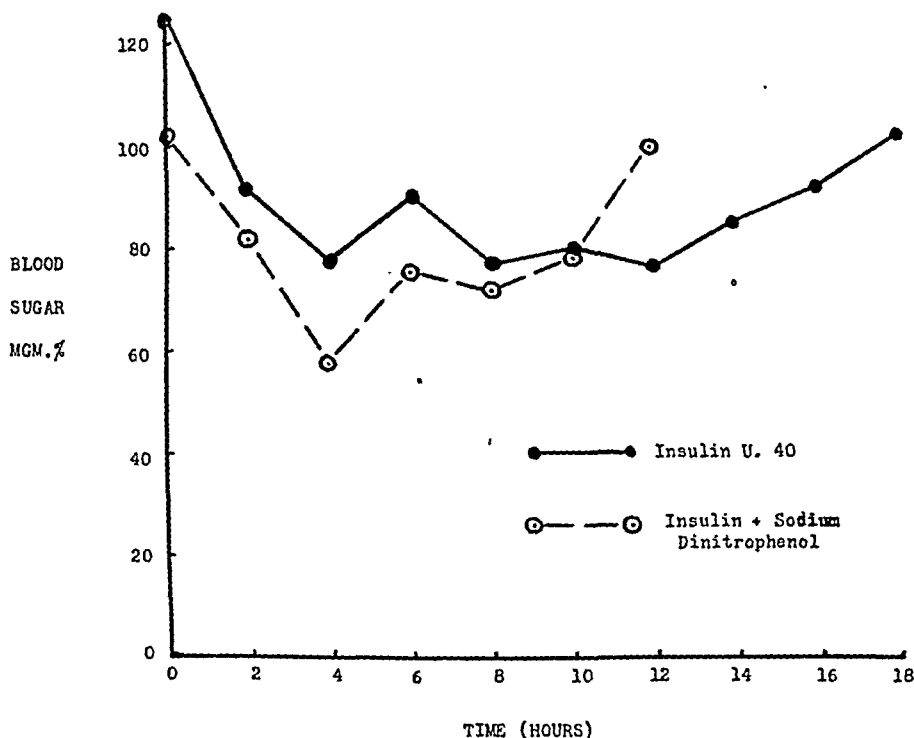


FIG. 4.—The blood sugar values, after 40 units of unmodified insulin were given to a patient with diabetes, are contrasted with those found after the same amount of insulin and a single dose of sodium dinitrophenol were given. In the former, the fasting level was regained in 18 and in the latter, 12 hours. The patient was afebrile throughout the experiment.

basal metabolism was reduced by medical treatment and partial thyroidectomy.

The conclusion reached from these studies, therefore, is that an increase in metabolism, physical exercise excepted, constantly produces shortening of the duration of action of insulin, with often a slightly greater depression of the blood sugar level. The action of sodium dinitrophenol in stimulating metabolism is a direct one on the tissue cells, and this effect can be demonstrated *in vitro* in isolated organs perfused with a dilute solution of the drug (Dodds

and Greville;⁴ Muntwyler⁶). For this reason, we feel that the results in both series of experiments have been produced by the increase in metabolism and that it is unlikely that an increased secretion of the anterior pituitary is responsible. Collip has isolated a specific metabolism-stimulating hormone from the pituitary, formed probably in the pars intermedia, which can increase metabolism in the absence of the thyroid and adrenal glands, and in the rat can abolish the hypoglycemic effect of insulin (O'Donovan and Collip;⁷ Collip²). In our experiments, an increase in metabolism had little effect on insulin hypoglycemia, but did produce a shortening of the duration of action of the insulin.

It is interesting to correlate these results with clinical findings in infections in diabetes. Often enormous doses of insulin are required to keep the blood sugar within normal limits, but the shortening of the duration of action is not by itself sufficient explanation for this, although it is undoubtedly of importance. Recently, in a mild diabetic with a urinary tract infection and gangrene, we found it necessary to give 50 units of insulin every 2 hours, or 600 units in the 24 hours; in order to control the diabetes, although after convalescence, no insulin was required. Here, obviously, some other factor or factors must have played a part—possibly an inactivation of insulin in the circulating blood by a trypsin-like enzyme derived from broken-down leukocytes in the infected areas, or else hypersecretion of the thyroid, adrenal, or anterior lobe of the pituitary.

Summary. 1. Alterations in metabolism in normal and diabetic subjects, produced by artificial fever and sodium dinitrophenol, have been shown to shorten the period of insulin activity, with little change in the actual degree of depression of the blood sugar. Other factors beside the fever and the increase in metabolism are necessary to produce the great insulin resistance found clinically in diabetic patients with acute infections.

2. These results give experimental proof of the advisability of giving frequent doses of insulin to diabetic patients with infections and fever.

The authors wish to thank Dr. William Wolff for supervising the laboratory work and Dr. Ferdinand Fetter for his cooperation in obtaining the hypertherm studies.

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CEVITAMIC ACID DEFICIENCY.

FREQUENCY IN A GROUP OF 100 UNSELECTED PATIENTS.

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THIS paper is the result of the study of the blood plasma cevitic acid concentrations in 100 adult medical patients in a general hospital. The first 100 individual determinations requested at the hospital laboratory were taken as a group and no selection of patients was made other than that occurring as the result of the varied interest of numerous attending men in ordering the determinations. The method of Farmer and Abt^{1,5} was used in making all determinations. Nearly all these estimations were made on private patients who were of an economic and social status that would presuppose a sufficiency of any desired diet.

In order to establish a normal plasma value as a point of reference in this investigation, the bloods of 50 student nurses in good health were checked. In this control group values from 0.60 to 1.12 mg. of cevitic acid per 100 cc. of plasma were found. The average was 0.81 mg. %. This is in general agreement with Farmer and Abt,¹ Rivers and Carlson,¹² and Portnoy and Wilkinson.¹¹

Deficient Group (38 Patients). As the study progressed it was found that a surprising number of very low values was being found in spite of the fact that all specimens were run within 30 minutes after the blood was drawn from the vein. This led us to consider a study of those that might be called definitely deficient in vitamin C to see if there were any particular clinical manifestations. With this in view we selected 0.40 mg. % (*i. e.* mgm. of cevitic acid per 100 cc. of plasma) as an arbitrary deficiency point. We discovered 38 patients below and 62 above this level. In this study, the 38 below 0.40 mg. % will be called the deficiency group.

In this deficiency group, 3 patients were in the range from 0.10 to 0.20; 16 in the range from 0.20 to 0.30 and 19 in the range from 0.30 to 0.40 mg. %. The lowest was 0.12 and the average 0.30. Twenty-five (66%) entered the hospital with a recent history or present symptoms of gastro-intestinal dysfunction or disease of a degree that had led to a diet definitely lacking in vitamin C content for from 1 month to 3 years. Of the remaining 13, 11 (26%) gave a very suggestive history of such deficiency, while but 3 (8%) gave a story suggesting adequate vitamin C intake (Table 1).

TABLE 1.—VITAMIN C INTAKE.

Diet.	Deficiency Group, 0.40 mg. % or below.		Normal Group, 0.40 mg. % and above.	
	No.	%.	No.	%.
Definitely deficient vitamin C intake	25	66	5	8
Suggestively deficient vitamin C intake	10	26	13	21
Adequate vitamin C intake	3	8	44	71

Note the % in each group on an adequate diet.

Of this group 15 (40%) had active peptic ulcers as their chief complaint and their plasma cevitic acid concentration varied from 0.12 to 0.40 (average, 0.31 mg. %). Thirteen (34%) had had recent active gastro-intestinal hemorrhage as evidenced by hematemesis or melena at the time of hospitalization or during the previous week. Their average plasma concentration was 0.27 mg. % (Table 2).

TABLE 2.—INCIDENCE OF PEPTIC ULCER AND GASTRO-INTESTINAL HEMORRHAGE.

	Deficient Group, 0.40 mg. % and below.	Normal Group, 0.40 mg. % and above.
Peptic ulcer	40%	5%
Gastro-intestinal hemorrhage*	34%	3%

* Nearly all of these hemorrhages were in ulcer cases.

An attempt was made to observe oral signs of vitamin C deficiency among these people. Sixty-four per cent had caries, spongy gums or well developed gingival infections. Thirteen per cent were edentulous, while but 24% had teeth and gums in good general condition. It is of interest to note that we found no mucous or epidermal petechiæ or suggillations (Table 3).

TABLE 3.—ORAL SIGNS OF VITAMIN C DEFICIENCY.

	Deficiency Group of 38, 0.40 mg. % and below.		Normal Group of 62, 0.40 mg. % and above.	
	No.	%.	No.	%.
Teeth and gums.				
Caries	12	32	4	6
Pyorrhea or spongy gums	12	32	2	3
Edentulous	5	13	4	6
Good condition	9	24	52	84

In reviewing the entrance blood counts we were unable to find any correlation of anemia with the low cevitic acid levels of the blood plasma. In 6 cases presenting a definite secondary anemia, but not clinical scurvy, the administration of 75 to 100 mg. of cevitic acid daily by mouth gave no reticulocyte response. This dosage may have been insufficient for such response, although such response has been reported by other workers in scorbutic anemias.^{3,4a}

The matter of final diagnoses made is of interest as they have a direct relationship to the dietary histories and vitamin C intake. Of the 38 cases in this deficient group, 32 (84%) had dysfunction or disease of the gastro-intestinal tract. Fifteen (40%) had active peptic ulcers. Only 4 instances of active infection were noted (Table 4).

TABLE 4.—FINAL DIAGNOSIS.

Diagnosis.	Cases 0.40 mg. % and below.	Cases 0.40 mg. % and above.
Peptic ulcer	15	3
Other diseases of the gastro-intestinal tract . . .	10	4
Cirrhosis of liver	3	1
Food allergy	1	4
Banti's disease	1	0
Pernicious anemia	1	3
Thyroid dysfunction	2	2
Drug addiction	1	0
Subdiaphragmatic abscess	1	0
Estrogenic deficiency	1	4
Chronic phlebitis	1	0
Nervous and mental diseases	1	16
Diseases of urinary tract	0	6
Acute respiratory tract infections	0	7
Cardiac disease	0	3
Arthritis—acute	0	5
chronic	0	3
Dermatitis (generalized eczema)	0	1

Non-deficient Group (62 Patients). In contrast to the findings of the deficient group are the remaining 62. Their average plasma cevitic acid was 0.71 mg. %. Considering the dietary histories, we find but 8% that could be considered definitely deficient and 21% suggestively deficient in vitamin C content, whereas 71% had been on adequate diets (Table 1). Here too, we find but 2 instances of recent gastro-intestinal hemorrhage, and both of these had cevitic plasma concentrations below 0.50. There were but 3 cases of peptic ulcer, with an average plasma content of 0.70 (Table 2). Only 10% had caries, spongy gums, or gingival infection; 6% were edentulous; and 84% of this group of 62 had teeth and gums in good general condition (Table 3).

Discussion. The conception of subclinical or asymptomatic states of vitamin deficiency is not new and yet such conditions are frequently overlooked because definitely deranged physiology or disease entities are not grossly demonstrable.^{2,10} Since this is so often true we were prompted to study these 100 patients in an attempt to determine the frequency of cevitic acid deficiency and its manifestations, if any. These people were a group which, because of their economic security, we suspected might have a very low incidence of vitamin deficiency. Thirty-eight per cent had less than half the normal concentration of cevitic acid in their blood plasma. In comparing these so-called deficient with the normal group it was found that gastro-intestinal dysfunction or disease was the greatest etiologic factor, being present in 84% of the deficient group. It is worth noting that economic ability to obtain a balanced diet is no indication that it is done. Such ability is far outbalanced by the fact that gastro-intestinal discomfort so commonly limits the range of foods eaten. Faulkner and Taylor⁶ among others have shown that infection has a decided influence upon depletion of the

No definite symptoms or signs of scurvy other than gingival sepsis and caries were detected, although plasma values as low as are seen in scurvy were encountered. This would seem to indicate that there may be some other factor than a cevitic acid deficiency involved in the etiology of scurvy as a clinical entity.

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BOOK REVIEWS AND NOTICES

THE GENUINE WORKS OF HIPPOCRATES. Translated from the Greek by FRANCIS ADAMS, LL.D., Surgeon. With an Introduction by EMERSON CROSBY KELLY, M.D. Pp. 384; 8 plates. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.00.

IN this volume are reprinted the translations of the "genuine works of Hippocrates" made by the Scottish surgeon, Francis Adams, at the request of the Council of the Sydenham Society and first published by the Society in 1849. The present edition by Emerson Crosby Kelly is itself apparently a page for page reprint of the "Works of Hippocrates" published in *Medical Classics* under Dr. Kelly's compilation in September, October and November, 1938, although the fact is nowhere stated in the bound volume. The two publications differ only in the appendage of an index to the latter. Dr. Kelly, in reprinting Adams' classic, has reproduced the translations verbatim, but has omitted most of the footnotes and all of the textual "argument" accompanying the translations in the original edition. A good deal of the flavor of the original Adams text has been lost in so doing; but, on the other hand, the editor has been quite successful in his purpose of presenting "a continuous and connected picture of medicine in the Golden Age of Greece." Each method has its value and the reader can return to the original Sydenham publication or the two subsequent reprints for Adams' scholarly annotations. Dr. Kelly wisely refuses to commit himself on the authenticity of the writings attributed to Hippocrates in the volume, and restricts himself to simple quotation of Adams' own recapitulation of his investigations as published in the first edition of the *Genuine Works of Hippocrates*. Dr. Kelly has removed the Oath from its previous position between the Aphorisms and the Law and replaced it with italicized emphasis at the opening of the translations. The Plate figures and accompanying explanations, which are divided in the two volumes in the original edition, appear as a single running series at the end of the present volume. The binding is handsome, and the paper and printing are excellent. E. L.

SHOCK AND RELATED CAPILLARY PHENOMENA. By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College; Director of Laboratories, Jefferson College Hospital, etc. Pp. 442; 30 illustrations and 5 charts. New York: Oxford University Press, 1938. Price, \$3.50.

DR. MOON has filled a real need with his book on shock in emphasizing the pathologic anatomy of this condition. The essential feature of shock is capillary stasis, most marked in the lungs and viscera. Microscopic examination shows acute edema and capillary hemorrhages with extravasations of blood into the lungs, liver, kidneys and intestinal mucosa. This capillary congestion produces the fundamental defect in shock, which is the loss of circulating blood volume.

There is no doubt about which one of the theories of shock the author endorses. He sets his banner aloft: "The only proposed explanation for shock with which these morphologic observations are compatible is that set forth under the considerations of Traumatic Toxemia." According to this concept there are formed in traumatized tissues certain toxins, similar to

histamine, which are absorbed into the circulating blood. These toxic substances are thought to cause dilatation and increased permeability of capillaries in other parts of the body. The process of segregation of blood from the circulation is thus initiated. This concept was advanced during the World War by Quénu and was supported by Cannon and Bayliss. It rested chiefly upon the close analogy between shock produced by trauma and shock produced by the injection of histamine. Attempts to demonstrate the presence of this hypothetical toxin in the circulating blood, however, have so far been unsuccessful and the majority of investigators today deny its significance in the production of traumatic shock.

Although he admits that proof for the toxemic hypothesis is lacking, Dr. Moon adheres strongly to it. Possibly too much space is accordingly given to detailed analysis of the shock which follows parenteral injection of toxic substances. Traumatic shock, the type seen after massive injuries, is not described.

With such emphasis on the toxemic theory, it is not surprising that insufficient attention is given to other aspects of shock which are generally recognized as significant. Although he accepts the fact that plasma and blood are lost into traumatized or inflamed areas, the author does not include this loss as one of the major causes of shock. Again, no emphasis has been placed on the nervous aspect of shock. In his discussion of the significance of emotion and pain, there is evidence of lack of understanding of the essential mechanisms involved. One of his statements is also open to question, that "shock can be produced when all nerve paths between the brain and the body have been severed."

The first five chapters of the book discuss capillary physiology and pathology. This review is good. When he attempts to interpret his observations on the morphology of shock in terms of capillary physiology, the author appears to be uncritical in accepting the opinions of other writers, especially if they coincide with his own ideas. There is no doubt about the reasonableness of his concept of shock but the picture may be a bit too facile. For instance, in his discussion of histamine he remarks, "Its very presence implies a physiologic purpose."

In his discussion of the evidence against the toxemic theory of shock, he brings out clearly certain objections to the experimental technique of other investigators, which it seems worth while to repeat: "(a) A decline in blood pressure is not an accurate criterion. (b) The deep narcosis used often causes low blood pressure and other shock-like manifestations. (c) Variable amounts of blood and fluid are lost incident to the trauma. (d) It is not possible to study minor degrees of shock nor to make later observations." It seems to the Reviewer that these criticisms of the work of others are valid. The author also states a principle for the evaluation of any concept of shock which, though truistic, may also be repeated. "Incompatibility with any established fact will invalidate any proposed explanation."

In spite of these rigid qualifications Dr. Moon is not especially critical of his own experimental methods. In his experiments "shock was induced without hemorrhage or trauma by introducing muscle substance intraperitoneally. . . . These methods eliminate deep narcosis and hemorrhage as factors"; yet in the same chapter he asserts: "Frequently shock follows an injury in which blood has been lost, and hemorrhage may be a grave complicating factor."

He frequently indulges in analogy. For instance, when he uses the phenomenon of local sweating to tie together urticarial wheals and the manifestations of shock, he makes the comment, "We have attempted no studies on the physiologic nature of this reaction but have assumed it to be a local phenomenon—this local perspiration supplies, then, another analogy between wheals and shock."

Dr. Moon has rightly emphasized that the phenomena of shock are present in many terminal conditions and I believe that he interprets these changes correctly as the result of anoxia, *i. e.*, inadequate oxygen supply to the tissues. When he states "that shock is merely the approach of death by the usual mechanism," there are few who would disagree.

On the practical side, he recognizes clearly that hemoconcentration takes place through loss of plasma from the circulation and that this concentration of the blood plays a dominant rôle in the production of shock. When, however, he advocates the use of determinations of hemoconcentration as the one best means for the clinical evaluation of shock, there are few who would follow him. Many feel that hemoconcentration may not be present sufficiently early and it may be lacking because of concomitant hemorrhage. He discards estimations of blood volume and blood flow because they are not sufficiently simple to be used, and yet he makes no mention of the volume of the pulse nor the temperature of the skin, clinical tests which have been used to evaluate the volume and flow of blood for centuries. He states that "experience indicates that hemoconcentration is the earliest detectible sign of shock." This may be so for the type of shock produced by intraperitoneal injection of muscle pulp or bile; but there is much doubt that this statement will hold true for all clinical cases of surgical shock.

As a definition of shock, Dr. Moon proposes the following: "Shock is a circulatory deficiency, neither cardiac nor vaso-motor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood." All clinicians will agree that a condition indistinguishable from surgical shock may be produced by coronary thrombosis; one example, at least, where shock is cardiac in origin. Again, experimental evidence indicates that shock can be produced by vasomotor activity. Perhaps, if the word "necessarily" had been inserted in the second clause of the opening sentence, the definition would be less open to criticism.

The service which Dr. Moon has performed is to bring into prominence the morphologic aspect of shock and to relate it to the physiologic defect of capillary stasis. Though both observations have previously been pointed out by Erlanger and his group, it is well that this essential fault should be emphasized.

N. F.

PRINCIPLES OF HEMATOLOGY. With 100 Illustrative Cases. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic, Cleveland; Formerly Professor of Experimental Medicine in the University of Kansas School of Medicine, Kansas City, Kansas. Pp. 348; 155 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1939. Price, \$4.50.

THIS new book on hematology emphasizes mechanism throughout. It is an attempt at simplification, designed for students and physicians. The opening chapters provide an admirably clear description of the normal and abnormal physiology of the hematopoietic system, with excellent photomicrographs and diagrams. Technical descriptions are limited to selected procedures. Marrow examination and supravital staining methods are omitted, although the estimation of hemoglobin by the iron content method is described in detail.

The clinical descriptions are incomplete. The hematological "entities" are merely limned and treatment is given but brief attention. Information concerning a given topic is sometimes to be found only by searching through various sections of the book. Complete information is sometimes lacking. For example, in the discussions of sickle cell anemia no differentiation is made from "sicklocytosis," nor is mention made that these conditions

occur almost exclusively in the negro. Again, ovalocytosis is used interchangeably with "oval cell anemia."

One hundred hematologic case summaries are presented in groups designed to illustrate differential diagnosis. While instructive, this arrangement results in considerable repetition. Cases of pernicious anemia are thus to be found under groupings headed "Clinical Classifications of Anemia," "Macrocytic Anemia," "Cryptic Anemia," and "Pernicious Anemia." One case protocol is headed "Macrocytic Anemia Due to Reticulocytosis," a title apt to introduce misleading ideas of etiology into the mind of the tyro.

This book is welcomed as a valuable addition to the modern hematologic library. It is an especially excellent summary of the hematologic "indices" that are now so popular. Your reviewer is old fashioned enough, however, to regret the lack of systematic rounded clinical discussion of specific subjects. A. C.

FAILURE OF THE CIRCULATION. By TINSLEY RANDOLPH HARRISON, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. Pp. 502; 61 illustrations and 22 tables. Second edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$4.50.

The principal change from the first edition has been the amplification of the discussion of angina pectoris. Such terms as "hypokinetic syndrome" and "dyskinetic syndrome," which were prominent in the first edition, have been largely replaced by simpler expressions such as "forward failure" and "backward failure."

The ideas of the author on certain controversial questions are more positive than those of many other students of the circulation. He expresses these ideas clearly. The book is therefore interesting and easy to read. C. W.

SEX and INTERNAL SECRETIONS. A Survey of Recent Research. Editor: EDGAR ALLEN, Yale University. Associate Editors: CHARLES H. DANFORTH, Stanford University, and EDWARD A. DOISY, St. Louis University. Twenty-seven Contributors. With Forewords by ROBERT M. YERKES, Yale University. Pp. 1346; 454 illustrations and 2 color plates. Second edition, entirely revised. Baltimore: The Williams & Wilkins Company, 1939. Price, \$12.00.

The first edition of this work in 1932, prepared by Dr. Allen at the request of the National Research Council's Committee for Research in Problems of Sex, was at once accepted as a most useful aid to workers in all branches of this field. Now after 7 years, a second edition has been subsidized by the Committee, requiring the addition of 400 pages, so rapid has been the progress in this particular field. The extent of the revision and amplification is revealed by consideration of the chapter bibliographies, in which more than one-half the references first appear in this edition. The great accumulation of specialized knowledge has required different authors for each of the 24 chapters, which are divided into 5 sections: 1, Biologic Basis of Sex; 2, Physiology of the Sex Glands, Germ Cells and Accessory Organs; 3, Biochemistry and Assay of Gonadal Hormones; 4, The Hypophysis and the Gonadotropic Hormones of Blood and Urine in Relation to the Reproductive System; 5, Additional Factors in Sex Functions and Endocrine Applications in Man. The first two of these occupy about two-thirds of the book. The authoritative statements cover all phases of the subject in a detailed and objective manner; human and comparative anatomy and physiology, experimental embryology, genic, endocrine and vitamin factors, the biochemistry of the various hormones,

problems of pregnancy lactation and the menopause, the sex drive, are among the subjects covered. Even a list, 4 pages long, of the various commercial preparations of the sex hormones is included. With such a wealth of exposition, it may seem hypercritical to object to compression of "the sex function in man" in a scant 60 odd pages. To be sure, observations on humans necessarily appear here and there through the book, but many practitioners, turning hopefully to this volume for help, will be disappointed to find, for instance, the menopause but briefly considered in a few pages and the prostate in little more than a page. The subject of treatment is properly handled with great caution; perhaps when the third edition appears, knowledge of the field will have sufficiently crystallized to permit a more definite presentation. Even so, none of those concerned with the investigation, teaching or clinical handling of the problems of sex can afford to do without this sterling volume. E. K.

VARICOSE VEINS. By ALTON OCHSNER, B.A., M.D., D.Sc. (Hon.), F.A.C.S., William Henderson Professor of Surgery and Director of the Department of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans, and HOWARD MAHORNER, B.A., M.D., M.S. (Surgery), F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans. Pp. 147; 50 illustrations and 2 color plates. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

This is a very pleasing little monograph. It has 19 chapters, 50 illustrations and 2 color plates. There is an interesting Foreword by Rudolph Matas to whom the volume is dedicated. It consists of an excellent brief history and brief but satisfactory sections on the anatomy, pathology and physiology of varicose veins. In the section of "Examination of the Varicose Vein Patient" the reader will find every test that is useful. The chapter on "Treatment" is divided into non-operative and operative sections. The Reviewer failed to find in this section a description of Linton's operation for dividing the communications between the deep and superficial veins, although he believes it is an important operation for those interested in the therapy of varicose veins. There is an excellent bibliography.

This monograph should prove to be a useful one to every surgeon interested in this condition. I. R.

ANGINA PECTORIS. Nerve Pathways, Physiology, Symptomatology, and Treatment. By HEYMAN R. MILLER, M.D., Attending Physician, Sydenham Hospital; Associate Attending Physician, Montefiore Hospital, New York City. Pp. 275; 39 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.25.

The author states that he prefers to consider angina pectoris as a paroxysmal upheaval of central origin, and this whether the individual has normal or abnormal coronary vessels. He says further that he cannot reconcile himself to a sharp distinction between coronary artery occlusion and so-called angina pectoris. Having this viewpoint he is interested in the neurologic and psychologic aspects of what he regards as angina pectoris. A great deal of attention is devoted to the innervation of the heart and great vessels and the pathways by which pain may be transmitted. A number of drawings are included which are designed to illustrate the anatomical relations of the nervous connections. Treatment is classified as non-surgical and surgical. To the Reviewer, such nomenclature seems to attempt to make the surgical tail wag the medical dog. C. W.

THE VAGINAL DIAPHRAGM. Its Fitting and Use in Contraceptive Technique. By LE MON CLARK, M.S., M.D., Chicago, Ill. Pp. 107; 53 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$2.00.

SINCE the first clinic opened in 1923, about 450 "birth control clinics" have been started in this country. Two obvious reasons for this appear. One is growing public interest in contraceptive help, the other is the existence of a method necessitating for each patient the detailed advice and instruction of an experienced physician. Probably 90% of all the clinics have spent most of their time teaching one method to most of their patients. Here is a small book about the "one method," the "method of choice" in clinics, a method which as patients and doctors learn of it is rapidly replacing other devices or procedures. It seems to have an "acceptability rate" in some private practice groups of well over 80%.

Lay interest and demand in this field have perhaps run faster than medical knowledge. Far too many women have received from the hand of a doctor, or from a druggist on prescription, a boxed diaphragm and brief verbal instruction about its use. But judgment in fitting diaphragms comes slowly by working with experts and by fitting and refitting many patients. Teaching the insertion and removal of a diaphragm takes patience and 10 to 30 minutes in the office. Teaching the further details of its use with due regard to emotional and psychologic hazards of the woman or the couple must also be done, done with tact and understanding not always had by young unmarried medicos. All this is made clear in the book, which is designed to teach the doctor how to fit and teach the patient.

The text is easy to read. About one-half of the 106 pages are good illustrations, either line drawings of the pelvis in section, or photographs of models or patients. These are probably the best teaching illustrations yet published. Watching another doctor work, getting the "feel" of how a clinic is run and patients are taught, is still the best education. But failing this, or in preparation for this, "The Vaginal Diaphragm" will be invaluable.

L. D.

FEVER AND PSYCHOSES. A Study of the Literature and Current Opinion on the Effects of Fever on Certain Psychoses and Epilepsy. By GLADYS C. TERRY, Research Associate in Neurology, Neurological Institute of New York, Columbia University; Formerly Research Assistant in Psychiatry, Henry Phipps Clinic, Johns Hopkins University. Pp. 167. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.00.

WHEREAS years ago infectious diseases frequently swept through unsanitary asylums, modern psychiatric hospital hygiene has deprived us of much valuable study material. The subject is discussed as follows: I, Introduction; II, Intercurrent Natural Fevers; III, The Clinical Use of Artificially Induced Fevers in Certain Nervous and Mental Disorders; IV, Therapeutic Implications. In these final pages, this tabular classification is given: Theories Favored by 106 Survey Contributors, Attempting to Relate Infectious Disease Phenomena and Changes in the Course of Certain Psychoses. There are six groupings, the largest showing 67 sponsors, for Restoration of Personality Balance Essentially Related to Psychological Alterations with Certain Biological Aspects Implied (57); 17 of these incline more specifically to "mobilization of personality resources redirected in a fight for self-preservation." Evidence for the most part shows that results of fevers induced by electrical devices is disappointing. Otherwise, throughout, there is insufficient unanimity of opinion to draw definite conclusions. To marshal data of this nature, understandingly, is admittedly difficult; but to have numbers, "I," "II," and "III," of tabular

digests, appearing more than once, with other tabular digests unnumbered, is neglectful. An exceptionally well-chosen foreign and domestic bibliography of almost 28 pages is a valuable feature of this monograph.

N. Y.

FUNDAMENTALS OF EXPERIMENTAL PHARMACOLOGY. By TORALD H. SOLL-MANN, M.D., Sc.D., Professor of Pharmacology and Materia Medica and Dean of the School of Medicine, Western Reserve University, Cleveland, etc., and PAUL J. HANZLIK, A.M., M.D., Professor of Pharmacology, Stanford University School of Medicine, San Francisco, etc. Pp. 307; 36 illustrations. San Francisco: J. W. Stacey, Inc., 1939. Price, \$4.25.

This is a completely revised new (second) edition of a well-known laboratory manual intended for medical students and their teachers. It contains useful directions for experiments and invaluable details of solution strengths and dosages; the dosages have been brought down to date in the revision, including sulfanilamide and the thio-barbiturates. The book can be recommended without reservation to teachers of pharmacology, but there is little in it for the average physician. As for students, the Reviewer's experience has been that unless careful selection of experiments is made from the large number described, bewilderment and dissatisfaction result, because there is too much detail and too little intellectual challenge for sustained interest and whole-hearted coöperation on the student's part.

C. S.

MANUAL OF TOXICOLOGY. By FORREST RAMON DAVISON, M.B., M.Sc., Ph.D., Assistant Professor of Pharmacology, College of Medicine, University of Vermont. With a Foreword by DAVID MARVIN, M.D., Professor Emeritus of Pharmacology, College of Medicine, University of Vermont. Pp. 241. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.50.

This book is intended to present, in compact form, the important facts concerning the diagnosis and treatment of those poisonings which the average physician is apt to encounter. In the Reviewer's opinion it lacks up-to-dateness, completeness, and accuracy to such an extent as to defeat its purpose. Thus, among the sources of lead poisoning, insecticidal sprays, leaded gasolines, and lead pipes are not mentioned; poisoning by barbiturates, fluorides, salicylates, acetanilid, and amino-pyrene receive no attention; while caffeine, conium, physostigmine and epinephrin—acute poisoning by any of which is not likely to be encountered by the average physician—are considered at some length. Among antidotal measures for acute cocaine poisoning barbiturates are not mentioned, nor are nitrites for cyanide or sodium formaldehyde sulfoxylate for mercury. In atropine poisoning the characteristic cerebral symptoms are not, as here stated (p. 117), "precisely those resulting from paralysis of the parasympathetic nervous system," and statements such as these (p. 99): "The effect of carbon dioxide on the system is to induce asphyxia by exclusion of oxygen—Death is caused by over-stimulation of the cerebrospinal system"—serve only to create unnecessary confusion. The index is unreliable: on looking up "sulfanilamide" one is referred to alcohol poisoning, and "hasheesh" leads one to war gases instead of cannabis.

C. S.

RÉTINE HUMAINE ET PHÉNOMÈNES ENTOPTIQUES. By DR. E. P. FORTIN. Pp. 207; 127 illustrations (3 in color). Buenos Aires: "Et Ateneo," n.d.

This monograph is essentially a correlation of some 60 odd papers the author has written over the past 30 years. He has always been opposed to the teachings of Cajal and his school with regard to the histology of the

retina. The author attributes Cajal's misinterpretations to the fact that he studied many vertebrate but few human eyes. He also believes that Müller's fibers which Cajal stresses are artefacts due to improper histologic technique.

To attempt to correlate entoptic phenomena with histologic studies is rather daring. However, as the author points out, one cannot regard the retina as a fixed mosaic and that the terms "discerning power" and "discriminating power" cannot be adhered to with the newer knowledge of retinal physiology.

There are many statements that physiologists will take exception to, such as "the ciliary muscle through its insertion on the internal limiting membrane exerts traction on the fovea" and may be an aid to fixation; and "the perceptive layer of the retina is not in the layer of rods and cones, but probably in the internal nuclear layer."

The monograph contains many beautiful photomicrographs of the retina, and should be consulted by all interested in the histology of the eye. Though the Reviewer does not agree with many of the author's conclusions, especially in the interpretation of some of the entoptic phenomena, the monograph is to be commended for its beautiful photography and the interest it may arouse for further study of "the most precious part of the human body."

R. McD.

THE PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY. VOL. II.

By H. B. VAN DYKE, Head of the Division of Pharmacology, Squibb Institute for Medical Research, New Brunswick, N. J.; Honorary Professor of Physiology, Rutgers University, etc. Pp. 402; 28 illustrations. Chicago: The University of Chicago Press, 1939. Price, \$4.50.

THIS is really an entirely new volume covering the literature subsequent to 1935, the first volume having covered the preceding period. The data are well selected, systematically arranged, presented in a readable and interesting manner, and illustrated by diagrams, graphs, and photomicrographs. At the end of each chapter the author summarizes the facts that he considers significant. This sound and scientific review should prove useful not only to those whose chief interests are in endocrinology, but to clinicians and research workers in other fields who wish to be familiar with recent developments in the anatomy, physiology and pharmacology of the pituitary body.

I. Z.

NEW BOOKS.

Cancer of the Colon and Rectum. Its Diagnosis and Treatment. By FRED W. RANKIN, B.A., M.A., M.D., Sc.D., F.A.C.S., Surgeon, St. Joseph's and Good Samaritan Hospitals, Lexington, Ky., and A. STEPHENS GRAHAM, M.D., M.S. (in Surgery), F.A.C.S., Surgeon, Stuart Circle Hospital, Richmond, Va.; Assistant Professor of Surgery, Medical College of Virginia. Pp. 358; 133 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.50.

Studies from the Center for Research in Child Health and Development, School of Public Health, Harvard University. II. Types, Levels, and Irregularities of Response to a Nursery School Situation of Forty Children Observed with Special Reference to the Home Environment. Vol. 4, No. 2, Serial No. 21. (Monographs of the Society for Research in Child Development.) By ELEANOR SLATER, with the assistance of RUTH BECKWITH and LUCILLE BEHNKE. Pp. 148; 7 illustrations, and 15 tables. Washington, D. C.: Society for Research in Child Development, 1939. Price, \$1.25.

Medical Vocabulary and Phrases. English, German, French, Italian, Spanish. By JOSEPH S. F. MARIE. Foreword by CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-Esophagology and Consultant in Broncho-Esophagologic Research, Temple University School of Medicine, Philadelphia. Pp. 358. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, \$3.00.

Architecture of the Kidney in Chronic Bright's Disease. By JEAN OLIVER, Professor of Pathology, Long Island College of Medicine; Pathologist, The Hoagland Laboratory; Formerly Professor of Pathology, Stanford University. Pp. 195; 59 text illustrations (some in colors); 23 plates; 16 stereograms. New York: Paul B. Hoeber, Inc., 1939. Price, \$10.00.

The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 11, Scarlet Fever to Testis, Undescended. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the Assistance in a Consultative Capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 730; 93 illustrations, 17 plates (6 in color). London: Butterworth & Co. (Publishers), Ltd., 1939. Price, \$12.00.

Fever Therapy Technique. By JACK R. EWALT, M.D., Resident Psychiatrist, Colorado Psychopathic Hospital; Instructor in Psychiatry, University of Colorado School of Medicine, Denver, ERNEST H. PARSONS, M.D., Captain, Medical Corps, United States Army; Neuropsychiatrist, Sternberg General Hospital, Manila, Philippine Islands, STAFFORD L. WARREN, M.D., Associate Professor of Medicine in charge of Division of Radiology, University of Rochester, School of Medicine, Rochester, N. Y., and STAFFORD L. OSBORNE, B.P.E., M.S., Associate in Physical Therapy, Northwestern University School of Medicine, Chicago. Foreword by FRANKLIN G. EBAUGH, M.D. Pp. 161; 16 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.50.

Diagnosis and Management of Diseases of the Biliary Tract. By R. FRANKLIN CARTER, B.S., M.D., F.A.C.S., Associate Clinical Professor of Surgery, New York Post-Graduate Medical School, Columbia University; Director of Surgery, Gouverneur Hospital, CARL H. GREENE, A.B., Ph.D., M.D., F.A.C.P., Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Clinical Professor of Medicine, Long Island College of Medicine, etc., and JOHN RUSSELL TWISS, A.B., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Assistant Physician, O.P.D., New York Hospital. Pp. 432; 84 illustrations and 6 plates. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

Headache and Head Pains. A Ready Reference Manual for Physicians. By WALTON FOREST DUTTON, M.D., Formerly Medical Director, Polyclinic and Medico-Chirurgical Hospitals, Graduate School of Medicine, University of Pennsylvania; Visiting Physician to Northwest Texas and St. Anthony's Hospitals; Director, Medical Research Laboratories, Amarillo, Texas. Pp. 301; 5 illustrations. Philadelphia: F. A. Davis Company, 1939. Price, \$4.50.

Roentgen Technique. By CLYDE McNEILL, M.D. Pp. 315; 268 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.00.

The Medical Clinics of North America, Vol. 23, No. 4 (Mayo Clinic Number, July, 1939). Pp. 284; 7 illustrations. Philadelphia: W. B. Saunders Company, 1939.

Die Katarrh-Infektion als chronische Allgemeinerkrankung. Eine dynamische Reaktions-pathologie des Rheumatismus und ätiologisch zugehöriger Erkrankungen als Ausdruck einer spezifischen Virusinfektion. By DR. MED. K. v. NEERGAARD, Professor an der Universität Zürich. Pp. 285; 24 illustrations. Leipzig: Theodor Steinkopff, 1939. Price, Paper, Rm. 11.25; Bound, Rm. 12.37.

Sleep and Wakefulness. As Alternating Phases in the Cycle of Existence. By NATHANIEL KLEITMAN, Department of Physiology, The University of Chicago. Pp. 638; 33 illustrations. Chicago: The University of Chicago Press, 1939. Price, \$5.00.

Man Against Microbe. By JOSEPH W. BIGGER, Sc.D., M.D., F.R.C.P.I., M.R.C.P. (LOND.), Professor of Bacteriology and Preventive Medicine, Trinity College, University of Dublin. Pp. 304; 16 illustrations and 18 plates. New York: The Macmillan Company, 1939. Price, \$2.50.

The Management of Tuberculosis in General Hospitals. Patients, Staff, Employees. Prepared by WILLIAM H. OATWAY, M.D., Assistant Professor of Medicine, University of Wisconsin Medical School; Assistant Physician, State of Wisconsin General Hospital, for the Council on Professional Practice of the American Hospital Association. Pp. 78. Chicago: American Hospital Association, 1939. Price, Paper, 50c; Cloth, \$1.00.

NEW EDITIONS.

Cancer of the Breast and Cancer of the Uterus. By MARION ELLSWORTH ANDERSON, A.B., M.D. Pp. 106; illustrated. Second edition. Clinton, Iowa: By the Author, 1939.

Manual of the Diseases of the Eye. For Students and General Practitioners. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York, etc. With the assistance of CHARLES A. PERERA, M.D., Instructor in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia University, New York. Pp. 515; 387 illustrations, including 31 plates and 95 colored figures. Sixteenth edition, revised. Baltimore: William Wood & Co., 1939. Price, \$4.00.

A Textbook of Bacteriology. The Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy, and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By HANS ZINSSER, M.D., Consulting Bacteriologist to the Peter Bent Brigham and the Children's Hospitals, Boston, and STANHOPE BAYNE-JONES, M.D., Professor of Bacteriology, and Dean, Yale University Medical School; Master of Trumbull College, Yale University, New Haven. Pp. 990; 16 illustrations. Eighth edition, revised and reset. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.00.

Recent Advances in Hæmatology. By A. PINEY, M.D., CH.B. (BIRM.), M.R.C.P. (LOND.), Assistant Physician, St. Mary's Hospital for Women and Children, London. Pp. 312; 34 illustrations and 8 colored plates. Fourth edition. Philadelphia, P. Blakiston's Son & Co., 1939. Price, \$5.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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PATHOLOGY OF THE INTERVERTEBRAL DISC.

IN recent years increasing interest has been shown in the pathology of the spinal column and in the correlation of the many lesions found with various clinical states. Until a few years ago there was very little exact knowledge concerning the morbid anatomy of the spinal column. Although much work had been done from a clinical and radiological standpoint, little of it rested on a firm pathological basis except for gross pathological disturbances. Schmorl^{40,41} of Dresden in 1925 instituted a brilliant series of investigations on the spinal column and in a very few years he had collected a large amount of material. From his work has emerged much important information. Until 1931 very little investigation along this line had been done outside of Germany. Probably the reason for this is the fact that in many countries it is not permissible, or at least not deemed prudent, to remove the spine at autopsy as a routine procedure. However, many excellent papers in English^{6,7,11,13,18,21,22,38,43,46} have appeared in recent years on the subject of pathology of the spinal column, chiefly with reference to the intervertebral disc. Although many of these papers have been discussions and interpretations of Schmorl's work, sufficient information on the pathology of the intervertebral disc has accumulated to warrant a review of this subject. The reviewer has examined approximately 600 spines removed routinely at autopsy in the Department of Pathology and Bacteriology of the University of Toronto, and in the following pages frequent references will be made to his own findings.

Various anatomical considerations are of great importance to the pathology of the intervertebral disc, and it may be well, therefore, to preface the body of this paper with a brief account of the development and anatomy of the vertebral bodies and other structures related to the intervertebral discs, as well as of the discs themselves.

Development and Anatomy of the Spinal Column. The intrauterine development of the spinal column was investigated by Bardeen² and was subsequently described fully by Compere and Keyes,^{13a} while the anatomy of the vertebral body and the component parts of the disc have been most completely described by Beadle.⁷

THE VERTEBRAL BODY. Each vertebral body arises from two centres of ossification, a cephalic and a caudal plate. In the new-born, the ossified part of the vertebra appears as a small ovoid mass. The total framework of the vertebral column is more largely formed of cartilage than of bone and the intervertebral spaces are of about the same size as the vertebral bodies. At this time the central ossified part of the vertebral body is separated from the vertebral arch by a rather broad plate of cartilage, the so-called vertebral arch epiphysis. This gradually disappears and the body of the vertebra fuses with the arch at about the 10th year. The vertebral bodies gradually increase in size and assume a rectangular shape.

At about 10 years of age the vertebral body from which the soft tissues and cartilages have been removed presents an appearance quite different from that of an adult. The upper and lower surfaces tend to be convex and are covered by a perforated bony plate. One of the most striking features presented by these surfaces at this stage is a series of radial grooves or furrows about the margin. These pass over the outer edge and extend for a short distance along the outer surface. They also extend in toward the centre of the vertebra, decreasing both in depth and breadth until they have completely disappeared in the central region. This structure of the infantile and adolescent vertebra has been particularly stressed by Schmorl as cited by Beadle,⁷ but it is not peculiar to the growing end of the vertebra. The same arrangement may be seen at the epiphyseal ends of the long bones.

Both articular surfaces of the juvenile vertebral body are covered by a cap of cartilage, around the margins of which, in the cartilage filling the depths of the furrows, small points of ossification begin to appear at about the 6th year. To the naked eye these centres are about 1 mm. in diameter and may be seen in a sagittal section if the plane of the section passes through the centre of one of the furrows. Schmorl and Junghanns⁴¹ investigated these centres of ossification by means of Roentgen ray examination of spines after they had been removed from the body. They came to the conclusion that the centres appeared between the 6th and 8th year in girls and between the 8th and 9th year in boys. They do not make their appearance at the same time all around the vertebral body nor in all segments of the spine. They are usually found in the deeper grooves first. The time of appearance of these centres as determined by other investigators varies from 11 to 15 years of age.^{16,20,30a,39} The results of all of these authors, however, were based on clinical Roentgen ray examination and are probably not as reliable as those obtained by Schmorl and Junghanns whose methods offered fewer technical difficulties.

These centres of ossification gradually enlarge and fuse to form a complete bony ring at about the 12th year. This ring in turn enlarges until it fills the grooves and ultimately becomes solidly fused with the vertebral body at about the 20th year. This fused epiphyseal ring is the so-called "Randleiste" of Schmorl. The furrows in the surface of the vertebral body extending centrally within the ring are gradually flattened out.

During the period of epiphyseal bone formation the outermost fibres of the annulus lamellosus (the fibrous ring forming the periphery of the intervertebral disc) become firmly anchored in the epiphyseal ring.

Whether or not the epiphyses play an important part in the growth of the vertebral body is a controversial point. Schmorl^{140d} and Beadle⁷ regard the epiphyseal ring of the vertebral body as being quite unlike other epiphyses because it does not contribute to the growth in height of the vertebra. However, it is the opinion of the reviewer, in agreement with Haas,¹⁹ that this ring should be regarded as an epiphysis fundamentally analogous to those found elsewhere in the body, but peculiarly adapted to its location and function. Endochondral growth of bone takes place at the attached surface of the cartilage applied to the superior and inferior surfaces of the body of the vertebra, and in the thick margins of this cap the epiphyseal ring appears which ultimately becomes fused to the body of the vertebra. A knowledge of the epiphyseal ring and its relation to the growth line of the vertebral body is of considerable importance in the interpretation of disturbances at the growth line.

The perforated articulating surfaces of the body of an adult vertebra are bounded peripherally by a complete ring of compact bone, the fused epiphyseal ring. This is raised considerably above the general surface of the vertebral body and gives the surface its typical concavity. The prominence of this ring varies in different regions of the spinal column, but it is never absent in a normal adult vertebra.

THE SPINAL LIGAMENTS. Extending anteriorly down the spinal column is a strong dense ligamentous structure, the anterior longitudinal ligament, which is firmly attached to the bodies of the vertebrae and to the intervertebral discs. Posteriorly, within the spinal canal, there is also a similar structure, the posterior longitudinal ligament, which is relatively weak, consisting of a series of fan-like bands attached to the posterior aspects of the intervertebral discs. Over the posterior aspects of the vertebral bodies it is narrow and thin and only lightly attached to the vertebrae. The lateral aspects of the vertebral bodies are also covered by ligamentous investments, but these are not sufficiently thick or well developed to warrant a special name.

THE INTERVERTEBRAL DISC. The intervertebral disc is a structure well adapted to the function it must perform. It serves as a bearing between the vertebrae by which pressure can be equally transmitted to the adjacent vertebrae and around which movement can take place. It also acts as a cushion by which the numerous small shocks of daily activity are absorbed. For purposes of description, the disc may be considered as being composed of three parts: a peripheral ring of fibrous connective tissue, the *annulus lamellosus*, surrounding a central pulpy mass; the *nucleus pulposus*; and thirdly, the cartilaginous plates covering the articular surfaces of the vertebral bodies above and below.

Übermuth⁴⁵ has carefully traced the development of the intervertebral disc which is derived in part from the notochord. The annulus appears in a cartilaginous matrix in the first few months after birth as a ring about the nucleus. With increasing age this ring grows in extent at the expense of the cartilage plate, from the periphery of which it originates. The outermost fibres become blended with the inner surfaces of the ligaments surrounding the spine and may be continued over the margin of the vertebrae to be firmly attached to the periosteum. As has been mentioned, other fibres around the periphery become firmly embedded in the epiphyseal ring of the vertebral body.

The annulus gives permanent form and size to the disc and is the seat of its strength and durability. It is composed of dense interlacing bands of collagen with a small admixture of elastic fibres. The annulus varies in size, strength and arrangement in different portions of the spine depending upon the functional demands of that particular segment.

The division between the annulus and the nucleus pulposus is not sharp, the one fading off gradually into the other, but the distinction between them is by no means artificial, since they are quite different both in structure and function. The nucleus forms a varying proportion of the intervertebral disc but it is never absent. It usually occupies a position slightly posterior to the center of the disc.

The nucleus pulposus stands out most distinctly in young individuals in whom degenerative processes in the disc have not yet begun. When the spine of a young subject is sawed through in the sagittal plane, the nucleus presents a very unique appearance and behaves in a manner quite different from the remainder of the disc. It protrudes from the cut surface as a small, rounded, glistening, pearly white eminence. On palpation it is found to be rather soft and elastic. The conclusion is obvious that before the column had been cut the nucleus must have been under considerable pressure. It has been stated by Schmorl^{140a} and repeated by many others that the nucleus when released springs forward because of its own elastic turgor. As the nucleus is composed of a semi-fluid (and hence non-compressible) substance relatively poor in elastic or collagenous fibres, it is difficult to conceive of it possessing any inherent elasticity or recoil. The nucleus is maintained under pressure by the elasticity of the fibres of the annulus, and during life by muscle tone and by the added pressure of the weight of the body on the spinal column. The turgor of the nucleus pulposus depends, therefore, on the integrity of the structures surrounding it.

Microscopically, the nucleus is composed of fine interlacing bands of connective tissue with a small admixture of elastic fibres. This tissue is very loose and contains in its meshes a highly fluid matrix, the water content of which is high. The strands are arranged in irregular bands and follow no set pattern except at the upper and lower surfaces where they are attached to the cartilaginous plates which are interposed between the nucleus and the adjacent vertebral bodies. In the meshwork of the nucleus are scattered various types of cells, fusiform or spindle-shaped connective tissue cells, groups of cartilage cells and occasionally, in young individuals, clear vacuolated cells which are thought to be surviving cells of the notochord. Peripherally the fibrous network gradually becomes dense, finally arranging itself in the thick curving bundles of the annulus fibrosus.

The articular cartilages are thin plates of hyaline cartilage separating the disc proper from the bony surfaces of the adjacent vertebral bodies. The cartilage plate covers only the perforated central area of the vertebral body and abuts on the elevated peripheral ring where the cartilage frays off into the fibres of the annulus. This layer of cartilage is cemented to the spongiosa, or cancellous bone of the vertebral body, by a thin layer of calcified cartilage. The cartilage plate is a relatively resistant structure of which one of the most important functions is to protect the spongiosa of the vertebral body which is provided with no end plate of compact bone.^{7,40a,b,c,e,f} Together with the annulus, the

cartilage plates also serve to maintain the normal form of the disc and to confine its tissue within normal limits.

The joints formed by the intervertebral discs differ greatly from other articulations of the body in that they allow a moderate degree of movement, flexion, extension and possibly rotation, but they possess no true joint cavities. Schmorl and Junghanns,⁴¹ in agreement with Luschka,²⁸ asserted that these joints do contain potential cavities which they believed they had demonstrated by means of injection of radio-opaque fluids. However, after studying gross and microscopic preparations and the illustrations of Schmorl and Junghanns, the reviewer is of the opinion that their positive results were due to artefacts produced by splitting and separation of the fibres of the disc by the injection fluid.

Übermuth⁴⁵ and Böhmig⁸ have investigated thoroughly the nutrition of the intervertebral disc. According to them, there are blood vessels arising from the marrow spaces which perforate the cartilaginous plates in early life. These undergo progressive obliteration until at the end of the growth period they have completely disappeared. The obliteration of these vessels may result in small scar-like defects in the cartilaginous plate and, as Schmorl^{40a} has pointed out, may give rise to points of weakness. The adult intervertebral disc contains no blood vessels. Its nourishment is entirely derived from the marrow by diffusion through the perforated bony end plate of the vertebral body.

Jung and Brunschwig²³ have investigated the innervation of the articulation of the vertebral bodies and have demonstrated sensory nerves in the anterior longitudinal ligament, but they could discover no nerve fibres in the intervertebral disc.

Pathology of the Intervertebral Disc. The spinal column is a skeletal organ complex in structure and unique in function. As well as acting as an encasement for the main pathway of the nervous system, it is the main support of the body. Due to the fact that man has assumed the upright position, the intervertebral discs, which are a part of the main weight-bearing joints of the spine, perhaps more than any other part of the skeletal system are subjected to the constant strain of functional activity. This wear and tear which is never in abeyance can bring about widespread structural changes which, in a large proportion of cases, cause no apparent disability. As a result, however, lesions which are associated with the decrescence of life are present in the spinal column to a degree surpassed in no other organ of the body.

CONGENITAL MALFORMATIONS. It is not intended to review here the many congenital malformations which affect the spinal column. However, brief mention will be made of certain developmental defects in the intervertebral discs which may form the basis for acquired lesions.

Nuclear expansions of the intervertebral discs are frequent and important pathological findings, especially in young individuals. They are probably of congenital or developmental origin. They vary considerably in size and are most common in the lower dorsal and lumbar segments of the spine. Typically they are hemispherical expansions of the nuclear portion of the disc into the spongiosa of the vertebral body. Frequently they occur on both sides of the disc; occasionally they are somewhat irregular. The cartilage plate is intact over these expansions but considerably thinned and these places must be regarded as points of weakness which may predispose to rupture of the plate under ab-

normal functional stress. Since these expansions are encountered at a very early age, it is difficult to conceive of them as being anything other than malformations of the discs. An alternative point of view, however, is that they occur at points of inborn weakness of the cartilage plates which gradually give way before the powerful turgor possessed by the nucleus pulposus in youth. These nuclear expansions of the intervertebral disc are of great importance in the etiology of adolescent kyphosis which will be discussed later.

Other findings which Schmorl^{40d} and Beadle⁷ consider as possibly developmental in origin are the small, jagged, fissure-like tears frequently seen in otherwise apparently normal cartilaginous plates. An explanation has been offered by Böhmig⁸ that these tears take place at the scarred site of the blood vessels which early in life penetrate the cartilaginous plates and which subsequently are obliterated. Since the reviewer has seen these changes only in microscopic preparations, he feels that they are probably artefacts due to the relatively greater shrinkage of the cartilage plate than of the bone in the process of dehydration.

CHANGES IN FORM OF THE INTRAVERTEBRAL DISC. Abnormal expansion or increase in height of the disc is a relatively infrequent change. The extraordinary expansile quality conferred upon the nucleus by the elasticity of the annulus can result in a bulging of the intervertebral disc into the adjacent spongiosa, if for any reason the resistance of the bone has been decreased. Senile osteoporosis is the condition in which this is most frequently seen, but it may also occur in other conditions in which there is softening or destruction of bone (multiple myeloma, Paget's disease, osteomalacia, osteoclastic tumor metastases, and so forth). The disc gradually bulges into the vertebra until it finally assumes the shape of a biconvex lens. A frequent end result of this expansion of the disc at the expense of the vertebral body is rupture of the cartilaginous plate, which has been stretched to its utmost limit, with resultant prolapse of the disc tissue into the spongiosa of the vertebra. On the other hand, expansion of the disc can become so marked without rupture of the cartilage plate that two neighboring discs will almost touch at their centres. The involved vertebræ show marked concavity of their articular surfaces. The expansion of the disc is not due to the formation of new tissue but merely to the taking up of additional water. In extreme cases this can lead to the formation of small cyst-like spaces in the centre of the nucleus.⁴¹ It should be pointed out that in order for such expansions of the discs to occur they must have retained to a considerable degree their elasticity. If degenerative processes have resulted in loss of turgor of the nucleus, expansion will not occur, no matter how great the weakening of the bony structure of the vertebral bodies.

Narrowing or thinning of the intervertebral disc is encountered much more frequently than expansion, and it may be taken as an axiom that thinning of an intervertebral disc means that that disc is the site of a pathological process.^{7,41} The loss of water content of the disc which occurs with advancing years, and the various types of degeneration which will be considered in detail later, may result in a decrease in its height. Frequently, combined with a narrowing of the intervertebral disc, there is a marked sclerosis of the adjacent portions of the bodies of the vertebræ. This is interpreted as being occasioned by the abnormal

movement allowed at the joint as a result of the slackness of the surrounding ligaments.

DEGENERATION OF THE FIBROUS TISSUE OF THE DISC. Changes which in other organs would be regarded as advanced degenerations occur in the intervertebral discs with astonishing frequency, and are initiated at a comparatively early age. That mechanical factors play a part is borne out by the fact that these lesions are more pronounced in those people who have been accustomed to hard manual labor rather than in those who have led a more sedentary life.^{7,41}

The most conspicuous difference between the spinal column of the aged or middle aged and that of the adolescent youth or young adult is the far inferior elasticity and softness of the intervertebral discs in the former. The nucleus no longer has the translucent appearance of youth, no longer swells forward on section and is not as readily differentiated from the annulus. The whole disc is converted into a more or less structureless mass. It has lost volume and is narrowed. Horizontal fissures in the substance of the nucleus are frequently seen. These alterations occur so regularly that it is difficult to decide when they cease to be a normal accompaniment of advancing age and pass over into really morbid changes.

Microscopically, with advancing years there is a gradual obliteration of the cellular elements of the disc and the fibres become more scanty and blurred, and finally disappear entirely. Only a diffuse pink-staining hyaline matrix remains. As an accompaniment of these changes, there is a gradual decrease in the water-content of the disc as was shown by Püschel.³⁷ She found that the nucleus of the intervertebral disc of a newborn child contained 88% water; in an old woman of 77, the water content was only 69%.

A form of degeneration which may be encountered at a relatively early age consists of a swelling of the nucleus region, which spreads gradually over into the fibres of the annulus. The disc in the affected area loses its firmness, and becomes dull grey and very friable. The strands of the annulus where they are involved appear dull and swollen. The tissue is loose and may be scraped away from the remainder of the disc with great ease. At a still later stage the whole disc substance, but especially the nucleus, is converted into a sodden, lumpy structure looking quite like lumps of porridge. At the same time large fissures appear in the central portion of the disc. These may spread out in a radiating fashion to involve the annulus to a considerable degree. There is, however, usually a ring of more or less well preserved annulus tissue around the periphery corresponding in position with its attachment to the epiphyseal ring. Microscopically, the degenerated tissue is without structure and stains diffusely pink with hematoxylin and eosin. Frequently, it contains an unknown pigment which varies in color from pale yellowish-brown to deep brownish-black. The nature of this pigment is quite obscure.

Another type of degeneration met with less frequently takes place characteristically in the anterior part of the annulus, chiefly in the mid-thoracic region. Lesions of this type are visible as small areas in which the tissue is converted into yellowish, dry, crumbling masses, measuring up to 7 mm. in diameter. Such areas, after the necrotic material has been removed, appear as small cavities in the annulus. These lesions are probably the basis for the condition of senile kyphosis which will

be discussed later. In connection with these areas of necrosis, small crescentic tears in the annulus very frequently may be seen; occasionally they may be stellate or radiating. They usually follow the inner margins of the epiphyseal ring.

As in other organs of the body, degeneration may be followed by calcification. Calcification of the discs in general has been discussed fully by Lyon²⁹ and Barsony and Koppenstein.⁵ Calcium nodes or areas of calcification of the nucleus pulposus are rarely seen and none have appeared in the spines examined by the reviewer. However, perhaps on account of their rarity and the recent interest in the subject, many individual cases have been reported in the literature. These were first described in the living by Calvé and Galland.¹¹ They appear on cross section as soft, pale yellowish-white, chalky masses in the nucleus.

Small irregular areas of calcification are fairly frequently seen in connection with the above mentioned areas of necrosis in the annulus. They occur most frequently in the anterior portion of the disc and vary in size from that of a pinpoint up to several millimetres in diameter. These are readily seen in Roentgen ray examination and may be mistaken for a non-union of the epiphyseal ring. These areas of calcification have a rather cloudy appearance in a Roentgen ray picture, as if the calcium has been precipitated on the preëxisting fibres. Microscopically, in decalcified preparations, the matrix is structureless and presents an appearance similar to other areas of degeneration or necrosis. These "primary" calcifications must not be confused with those which may occur secondarily following inflammatory conditions such as tuberculosis.

Hemorrhages, old or recent, are occasionally to be found in the intervertebral disc and usually occur in degenerated portions. It is probable that these hemorrhages are traumatic in origin, arising when injuries to the cartilage plates allow blood to enter from the marrow spaces.

PATHOLOGICAL CHANGES IN THE CARTILAGE PLATES. The degenerative changes above described may be limited to the disc tissue proper but more frequently they involve also the neighboring structures. The cartilage plates are relatively resistant but they are subject to a series of pathological changes, some of which are primary but most of which are further developments of the degenerative processes commencing in the fibrous parts of the disc as already described.^{7, 40a, b, c, e, f} Destructive diseases of the spongiosa of the vertebral body may lead to partial or complete dissolution of the cartilage plates, but it is astonishing how much resistance to destruction is offered. This is particularly well shown when the vertebral bodies are involved by secondary carcinoma. The spongiosa may be largely occupied by tumor and yet the cartilage plates may be in an extraordinarily good state of preservation. The expansion of the disc and stretching of the cartilage plates in osteoporosis have already been mentioned.

Tears and ruptures of the cartilage plates are encountered occasionally in the spines of young individuals in association with nuclear expansions of the disc and thinning of the cartilage over these expansions as described in a previous section of this review. It is at the points of greatest thinning of the cartilage that ruptures most frequently occur. These tears are extremely difficult to account for. To explain them as the result of degeneration of the cartilage does not

seem reasonable because, apart from the rupture, the plates show none of the characteristic changes of degeneration. A most plausible explanation is that these cartilages are the seat of a congenital fault in texture and that functional strains of unusual severity cause them to tear or rupture.^{40d} A feature which lends support to the theory of congenital weakness is that these ruptures or tears occurring in young individuals usually are found in the cartilages of several vertebræ. The tears may be linear or may take a stellate form. They occur characteristically in the region opposite the nucleus pulposus but may be found anywhere in the cartilage plate.

Similar tears may occur in the cartilage plates in middle life or later, not because of innate weakness of construction, but as an integral part of the senile degenerative processes which affect the fibrous portion of the intervertebral disc. Senile degeneration of the cartilage is almost as common as the corresponding changes in the disc proper, and may lead to marked alterations.

The characteristic senile changes which appear in the cartilage plates are best seen microscopically. The fibres of the cartilage appear frayed and broken. Commonly the matrix does not stain well and presents a moth-eaten appearance. The plate is split into many layers so that there are multiple small horizontal fissures which form slit-like spaces in the substance of the plate. It may be extremely thinned out and even ruptured at one or many points. In the latter case, much of the cartilage plate may be destroyed, being represented only by small islands of cartilage scattered along the original line of the plate.

These ruptures or breaks of the cartilage plates usually result in the escape or prolapse of disc tissue into the spongiosa of the vertebral body. However, if the degenerative changes in the cartilage develop gradually and there is no abrupt rupture of the plate, a reactive process takes place in the adjacent bone which prevents the occurrence of prolapse. Then, one frequently sees the fibrous tissue of the disc resting directly on a dense layer of compact sclerotic bone with only a few small remnants of the cartilage plate interposed at intervals.

PROLAPSE OF DISC TISSUE INTO THE SPONGIOSA. When the cartilage plate gives way, an escape or prolapse of the tissue of the nucleus pulposus into the spongiosa of the vertebral body frequently follows. In the great majority of cases the lesions so produced evoke no clinical symptoms but they are frequently associated, particularly in older individuals, with marked deformities of the intervertebral discs and of the spinal column as a whole. The occurrence of such prolapses apparently plays a fundamental rôle in the etiology of adolescent kyphosis which will be discussed in detail presently.

Prolapses of the tissue of the intervertebral disc had been seen and described by Luschka²⁸ in the middle of the 19th century. They were rediscovered by Schmorl^{40a} who described their mode of development and interpreted their significance. They occur typically when there has been a break in the cartilage plate as described in the preceding section. This break allows the substance of the nucleus pulposus to push its way out into the spongiosa of the vertebral body. This is accomplished by the normal turgor of the nucleus in the young and by the pressure occasioned by continual activity in the aged in whom the turgor of the disc is lost. The foreign tissue fills the marrow spaces of

the spongiosa and causes atrophy of the bony trabeculae with gradual enlargement of the prolapse until a state of equilibrium is reached.

In sagittal section of the vertebral column the masses of prolapsed tissue appear as small, firm, white or bluish white, sharply circumscribed nodes in the spongiosa. They vary in size from that of a pin-head to over 1 cm. in diameter. They occur in close proximity to the disc but may appear to have no connection with that structure. However, if serial sections are studied, a communication is always found. Seen in three dimensions, the prolapsed tissue appears as a small mulberry-like mass connected by a narrow or broad pedicle through a gap in the cartilage plate with the nucleus of the intervertebral disc.

In young individuals, prolapses of disc tissue occur typically in a whole series of vertebrae. They are of a bluish-white color, firm and quite different in appearance from the remainder of the disc. This is due to the formation of cartilaginous tissue which occurs as a reactive process. Cartilage formation begins at the margin of the prolapsed tissue and gradually extends inward. The name "cartilage node" was given to these structures before their exact nature was known and for this reason they are referred to in many places as "cartilage nodes" or, more recently, as "Schmorl's nodes."

In the course of time, new bone is formed as part of the reaction and the prolapsed disc tissue becomes surrounded by a layer of compact bone. Prolapses of long standing may always be recognized by the presence of this shell of compact bone about the node, and it is this bony shell alone which renders the node recognizable in Roentgen ray examination.^{40a,41} This layer of new bone tends to prevent the further extension of the prolapse. The reactive or reparative processes described occur most readily and reach their highest development about nodes of prolapsed disc tissue in the spines of young individuals.

In middle aged and elderly persons in whom the turgor of the intervertebral discs is diminished, breaks in the cartilage plates still permit the escape of disc tissue which is gradually pressed out into the spongiosa by the pressure of the weight of the body, muscle tone and functional activity. Isolated discs in the spinal column are usually involved, rather than a whole series as in young people. The breaks in the cartilage plates which permit the prolapse of disc tissue are usually the result of senile degenerative changes in the cartilage. Large segments of the cartilage plate on one or both sides of the disc may have disappeared leaving only small fragments of cartilage which may be considerably displaced into the spongiosa. These fragments of cartilage thus form an irregular and interrupted boundary between the vertebral body and the intervertebral disc. Under these conditions, due to the fact that degeneration of the cartilage takes place rather slowly and that the nucleus pulposus has already lost most of its turgor, the prolapses of disc tissue, though extensive, do not penetrate deeply into the spongiosa. An examination of such prolapses gives one the impression of soft dough being forced through a sieve.

The usual sequel to the development of these prolapses in middle life and old age is not the stimulation of new cartilage and bone formation but vascularization and eventual cicatrization both of the prolapsed tissue and the adjoining intervertebral disc. Blood vessels grow in from the spongiosa and gradually destroy the prolapsed tissue. At the same time, newly formed blood vessels penetrate the intervertebral

disc, forming a rich plexus and converting large parts of the disc into granulation tissue. This tissue, in the course of time, is converted into tough scar tissue. Such areas are commonly found in the examination of the spinal columns of elderly persons. When the affected intervertebral disc is cut across, areas of granulation tissue may be found appearing as dark red, soft, spongy masses lying in the substance of the disc tissue usually in the region of the nucleus. In a disc in which this process has advanced to the formation of scar tissue, much of the disc is found to be replaced by large patches of tough greyish-white sunken tissue. The final outcome of this process may be solid fibrous union between two adjacent vertebræ with marked narrowing of the intervertebral space so that little if any movement is possible. In some instances bony trabeculæ grow from the spongiosa into the disc following the advance of the blood vessels and connective tissue. In this manner part or all of the disc may become ossified with the final development of bony union between the vertebral bodies. Ossification of the anterior part of the intervertebral disc occurs characteristically in association with senile kyphosis, while ossification in all parts of the disc occurs to a marked degree in Bechterew's type of spondylitis. Both of these conditions will be described in detail presently.

In a statistical study of prolapses of disc tissue into the spongiosa, Schmorl^{40a} found that they occurred in 38% of a group including all ages. Under the age of 60 the ratio between men and women was about 2 to 1, but above the age of 60 this ratio was reversed. He explained the higher incidence in men under 60 as the result of the heavier work performed by them during the active period of life. The reversal of the ratio after the age of 60 he accounted for by the fact that women continue to be physically active, since they bear the burden of house work, long after men have retired from active labor.

POSTERIOR DISPLACEMENT OF DISC TISSUE. The clinical importance of posterior displacements of intervertebral disc tissue is reflected in the large number of papers on this subject which have appeared in the past few years. Early reports by Stookey,⁴⁴ Dandy,¹⁴ Bucy¹⁰ and Elsberg¹⁷ described these lesions as chondromata or small cartilage growths arising from the posterior surface of the vertebral bodies and causing compression of the spinal cord. However, it remained for Schmorl and his pupils to elucidate the true nature of the lesions. The so-called chondromata are, in fact, posterior prolapses of nuclear tissue of the intervertebral disc protruding into the spinal canal. In recent years numerous papers on this subject have appeared in the literature.^{3,4,15,25a,b,c,26,27,31-36,47} The syndrome resulting from pressure of the displaced tissue on the spinal cord and on the nerve roots has been elucidated and the relationship of the lesion to certain types of sciatic pain has been pointed out. However, these publications have dealt chiefly with clinical problems and they have added nothing of fundamental importance concerning the pathology of the condition.

Andrae¹ made a thorough pathological study of these posterior displacements of intervertebral disc tissue. He was able to find them in 15% of spinal columns examined routinely at autopsy. This seems an extraordinarily high incidence, but it must be borne in mind that it is relatively rare for the prolapse to attain sufficient size to cause compression of the spinal cord. Moreover, the most frequent site of these lesions is in the lower thoracic and upper lumbar regions where the

spinal canal is considerably larger than the part of the spinal cord which it must accommodate. These posterior displacements of disc tissue occur chiefly in the later years of life and are rarely found before the age of 30, since they have their origin in the degeneration of the annulus of the intervertebral disc which accompanies advancing years. In many cases in which the displacement of disc tissue has caused symptoms, there is a history of trauma.^{26,47}

Posterior extrusions of intervertebral disc tissue may be exposed to view by sawing through the pedicles of the vertebral arches so as to lay open the spinal canal. After removal of the spinal cord, the nodules of displaced tissue may be seen on the posterior aspect of the intervertebral discs or vertebral bodies. They are usually situated at or near the level of an intervertebral disc, but occasionally they apparently arise at some distance from a disc. They appear as bluish-white, firm nodules, varying in size from that of a small wheat grain to that of a bean, shining through the posterior longitudinal ligament by which they are covered.

The intervertebral disc from which the extruded tissue originates usually shows some degree of degeneration. The posterior part of the annulus always shows degenerative changes and, if serial sections are cut, fissures or tears can be found in it, through which the tissue of the nucleus pulposus gains its exit. The break in the annulus is frequently very small and difficult to locate. The extruded tissue appears under the posterior longitudinal ligament or occasionally among its fibres. It may burrow between the ligament and the posterior surface of the vertebral body for some distance before it forms a nodule and this explains the situation of those nodules which appear at some distance from the intervertebral disc. Microscopically, the displaced tissue has an appearance characteristic of the nucleus pulposus but there is a rich admixture of cartilage cells.

These posterior displacements of disc tissue rarely give rise to lipping of the vertebræ or to the formation of osteophytes. This is probably due to the fact that the posterior longitudinal ligament is but weakly attached to the vertebral bodies so that no great degree of tugging or irritation of the periosteum is occasioned by the presence of the extruded tissue.

Severe trauma may cause sudden and extreme posterior displacements of the intervertebral disc. In such cases the posterior part of the disc is torn and, while the cartilage plates remain intact, the greater part of the disc is extruded into the spinal canal. Great compression of the spinal cord usually results unless the displacement occurs in the lower lumbar region.

ANTERIOR AND LATERAL DISPLACEMENT OF DISC TISSUE. Frank and readily recognized anterior or lateral displacements of intervertebral disc tissue are found rather infrequently. When they do occur they appear as firm nodular swellings of various sizes in the neighborhood of the intervertebral disc. More detailed reference to them will be made presently in the discussion of spondylosis deformans.

THE RÔLE OF TRAUMA. It is scarcely possible to over-emphasize the importance of trauma in the etiology of the various lesions of the intervertebral discs, if one is permitted to include under the term not only the sudden severe injuries, which cause obvious gross damage,

but also the slight shocks to which the spinal column is subjected in the course of normal physical activity. In the young, trauma of the latter kind may be responsible for rupture of the cartilage plates, if these be not of normal strength and thickness. This may be followed by a whole series of events, in which trauma plays a part, leading to marked spinal deformity. In middle and later life, enormous damage is done by hard physical work to the less resistant discs which in early life would have stood the strain readily. It is possible that the degenerative processes which accompany advancing years may themselves be the result of the incessant wear and tear of a life-time of functional activity. It is significant in this connection that the more severe spinal deformities of later life which are dependent on degenerative changes in the intervertebral discs are found predominantly among manual laborers and occur more frequently in men than in women.^{7,40a,c,d,41}

The more violent injuries which cause fractures of one or more vertebral bodies must be put in another category. It is not within the province of this review to discuss the many and varied types of fractures of the spine and the possible resultant injuries to the intervertebral discs.

INFECTIONS. Infectious spondylitis can be caused by a wide variety of organisms in addition to the tubercle bacillus. Such infections involve primarily the bony structures. Since the intervertebral disc after adolescence is normally lacking in blood vessels and has not been shown to contain any lymphatics, it is readily understood that the disc is rarely affected primarily by infections and, indeed, is only involved and destroyed after there has been considerable destruction of the adjacent bone.¹²

TUMORS. If one excepts the chordomas which occasionally arise in the occipital and sacral regions, primary tumors of intervertebral disc tissue are unknown.

The Relation of Spinal Deformity to the Intervertebral Disc. Up to this point in this review no attempt has been made to discuss the effects of lesions of the intervertebral discs on the spinal column as a whole. The large and important group of scolioses can be excluded from such a discussion, since this type of deformity is not dependent on primary changes in the intervertebral discs. All types of scoliosis except those due to congenital malformations are caused by extrinsic factors and the intervertebral discs play no part in their etiology. But the discs may be secondarily affected, as Calvé and Galland¹¹ have pointed out. There is usually a lateral shifting of the nucleus pulposus to the side of the convexity of the curve.

On the other hand, changes in the intervertebral discs which are believed to be of fundamental etiological importance are found typically and constantly in association with various other simple deformities, notably the kyphosis of youth and age, and the group of senile degenerative changes which constitute the condition known as spondylosis deformans or osteoarthritis of the spine. The clearest single entity is that of adolescent or juvenile kyphosis which may be separated quite readily from the remainder.

ADOLESCENT KYPHOSIS. Adolescent or juvenile kyphosis is a gradually developing, insidious type of kyphosis which appears chiefly in boys in the adolescent period of life. The kyphosis forms a sweeping curve

most commonly in the middle and lower thoracic regions. Radiologically there is a characteristic wedging of the vertebral bodies and irregularity of outline of their ends.

The condition was first described and isolated as a clinical entity by Scheuermann³⁹ in 1921. Since then many discussions of the disease have appeared in the literature with various explanations of the underlying pathological condition.^{9a,b,16,24,30a,b} It was generally thought at first that the disease is caused by a morbid process at the growth line between the vertebral epiphysis and the vertebral body, similar in character to the osteo-chondritis of Legg-Perthes' disease,^{9,30} but this view is controverted by the studies of Schmorl.^{40d} Pathologic investigations of the disease are particularly difficult because the kyphosis in question is not dangerous to life and recourse must be had to post mortem examination of the few patients who chance to die in early life from intercurrent disease. In those who die later the original process is so overshadowed by subsequent changes that correct interpretation is virtually impossible. Schmorl,^{40d} however, collected several cases and made a thorough investigation of the morbid anatomy of the disease. He reached the conclusion on the basis of these studies that a series of prolapses of disc tissue into the spongiosa was the underlying cause. The reviewer had the opportunity of studying 1 case, that of a youth who died of typhoid fever 1 year after the onset of kyphosis, and he was able to substantiate Schmorl's conclusion.

When the spinal column from a case of adolescent kyphosis is examined, the most striking pathological feature, apart from the kyphosis itself, is the presence of multiple prolapses of intervertebral disc tissue into the spongiosa of a whole series of vertebral bodies. These lesions usually reach their greatest severity at the apex of the abnormal curvature. The prolapses may occur at either surface of the disc, or frequently at both surfaces and there may be as many as two or three on each side. They occur typically in the region of the nucleus pulposus and have the typical appearance of prolapses occurring in youth as described in a preceding section of this review. Different areas of prolapse show varying degrees of repair. One of the most important features, which is seen microscopically, is the complete disappearance of the cartilage plate in the areas involved and its entirely normal appearance elsewhere.

The basis for the formation of these multiple prolapses of disc tissue is the rupture of the cartilage plates in a whole series of intervertebral discs. The conditions and the sequence of events which lead to the occurrence of rupture of the cartilage plates are extremely difficult to determine. Schmorl^{40d} has postulated a congenital weakness of the cartilage forming the plates. The fact that the spines of many adolescents show an expansion of the disc in the region of the nucleus with stretching and thinning of the cartilage plates lends some support to his theory. A congenitally weak plate of cartilage, thinned out by stretching, might be ruptured by the added strain of increased muscular activity which normal cartilage plates could easily withstand. This idea is further supported by the typical clinical history, for as Scheuermann³⁹ pointed out, this type of kyphosis frequently has its inception shortly after the adolescent youth has taken up arduous manual labor. In Germany, the condition is frequently spoken of as "apprentice-

kyphosis" (Lehrlingskyphose). An alternative possibility is that an isolated severe trauma may cause the rupture of a series of weakened cartilage plates simultaneously. There is every reason to believe that this may occur without fracture of the vertebral bodies.

The gradual development of kyphosis is the logical outcome of a series of events which follow the occurrence of rupture of the cartilage plates. There is a certain loss of disc substance, due to the formation of multiple prolapses, with consequent loss of turgor of the discs and narrowing of the intervertebral spaces. Since the small posterior joints of the spinal column act as a fulcrum at each intervertebral articulation, this narrowing is more pronounced anteriorly than posteriorly. It must be remembered that this process begins during a period of active growth when endochondral formation of bone is still progressing on the side of the cartilage plate applied to the vertebral body. Ruptures of the cartilage plates and the development of prolapses of disc tissue cause considerable disturbance in the process of ossification. This, combined with the increased pressure on the anterior portions of the vertebral bodies due to partial collapse of the discs, results in a cessation of growth of the vertebræ anteriorly and leads eventually to the formation of wedge-shaped vertebral bodies since growth continues at their posterior margins. If several vertebræ are involved, this wedging of the vertebral bodies together with flattening of the intervertebral discs need not be great to produce a pronounced kyphosis. In agreement with Schmorl,^{40a} the reviewer found the epiphyseal ring little involved in this process.

The dense irregular line seen in Roentgen ray examination at the articular surfaces of the vertebral bodies is caused by the reactive formation of compact bone about the nodules of prolapsed disc tissue. After a state of equilibrium has been reached this compact bone may become rarefied and the shadows may almost disappear.

SENILE KYPHOSIS. The characteristic feature of senile kyphosis is the curvature itself which is merely an exaggeration of the normal dorsal curve. In a pure case the greater part of the intervertebral disc is well preserved, the various forms of senile degeneration are present only to a minimal degree, and the cartilage plates are intact. There are, however, changes in the anterior portions of the discs and adjacent portions of the spongiosa which are most marked in the region of the greatest deformity. In the involved regions in advanced cases there is complete destruction of the anterior portions of the intervertebral discs and the gap between adjacent vertebræ is bridged by bony tissue. The remaining parts of the discs may appear quite normal. The anterior portions of the vertebral bodies adjacent to the bony bridges usually show a definite sclerosis, the bony trabeculæ being dense and more closely set.^{24, 41}

The development of this condition usually begins with the appearance of the small areas of degeneration which occur in the anterior portions of the discs as has been already described. This results in a narrowing of the discs anteriorly and, consequently, the anterior margins of the vertebral bodies more closely approach one another. With the decrease in the cushioning effect of the discs in this region and the abnormal mobility, there is a malarticulation of the adjacent surfaces of the anterior parts of the vertebral bodies. This is followed by sclerosis and overgrowth of the bone which gradually increases in extent until the

anterior part of the intervertebral space has been completely bridged across. In advanced cases, the spine is completely ankylosed in the region of the kyphosis.

Senile kyphosis differs from that of adolescence in that it appears in the upper or middle dorsal region. The youthful form is found much lower, in the middle or lower dorsal segments. In senile kyphosis, the shape of the vertebral bodies is modified so that they are higher posteriorly than anteriorly, but this change does not occur to nearly so marked a degree as in the adolescent form. In senile kyphosis the wedge formation cannot occur as a result of disturbance of growth. In this instance, therefore, it is necessary to postulate a decrease in height of the anterior portion of the vertebral bodies, occurring concomitantly with the sclerosis and re-arrangement of bony trabeculae. This wedging of the vertebrae does not, however, play an important part in senile kyphosis; in many cases the anterior narrowing of the disc is sufficient to account for the deformity.

SPONDYLOSIS DEFORMANS. The whole series of senile degenerative lesions of the intervertebral discs described in a previous section of this review forms a continuous progression of events, the total of which may be considered as the fundamental lesion of spondylosis deformans or osteoarthritis of the vertebral column. Spondylosis deformans is, then, the typical senile disease of the spinal column and its origin may be traced to a generalized degeneration and dissolution of the intervertebral discs. It may occur just as early as degenerative changes are present in the discs to any considerable degree. In advanced cases of spondylosis deformans there is almost always an associated kyphosis. This, however, is not to be regarded as an integral part of the disease but rather as a co-existent senile kyphosis.

The presence of osteophytes or lipping of the vertebral margins is the most characteristic feature of spondylosis deformans. These structures take the form of jagged ledges or shelves protruding from the articular margins of the vertebral bodies and usually occurring in pairs, one on each of the adjacent vertebrae. They occur most commonly on the antero-lateral aspect of the bodies of the vertebrae just lateral to the anterior longitudinal ligament. They may be single or scattered but usually form a row. The most frequent situation of these osteophytes is the mid-thoracic region on the right side and in the lumbar region on the left. That is, they tend to occur in the concavities of the physiological scoliosis which is present to a slight degree in almost every spine. In right-handed individuals there is generally a slight physiological scoliosis with its convexity to the left in the mid-thoracic region, and osteophytes are formed on the right side of the column in that segment. Their distribution in the lumbar region is apt to be more irregular and they frequently occur on the anterior aspect of the lumbar vertebrae. Shore⁴² found that osteophytes occurred less frequently at the "anti-clinical" points in the spine, that is, at those points through which a plumb-line would fall in the erect position. At these points the vertebrae are supposed to be balanced with a minimum tendency to irregularity of movement.

The osteophytes first appear as small bony outgrowths from the lateral surface of the vertebral body just below the outer margin of the epiphyseal ring, at which point the ligaments surrounding the spine are strongly attached to the periosteum. Bony union between osteophytes from

adjacent vertebræ is common, but is not the usual end result. More often they touch and interlock in a tooth-like manner leaving a small space filled with cartilage and degenerated disc substance between them. In this way they achieve at least a functional union. In the course of time they may grow to an enormous size, the paired projections from adjacent vertebræ forming large bony tumors chiefly on the lateral aspects of the spinal column.

Schmorl^{140c} has remarked that lipping of the vertebral bodies or the formation of osteophytes never occurs in the presence of normal intervertebral discs and this has been amply corroborated in the studies of the reviewer. The manner of formation of the osteophytes is probably somewhat as follows. The progressive senile degeneration of the intervertebral disc and especially its annulus, with consequent loss of turgor and cushioning effect of the disc, allows an abnormal mobility between the vertebral surfaces; and during the movements of ordinary activity, the disc tends to bulge slightly at the periphery, pushing outward against the ligamentous structures surrounding the spine. This in turn exerts a tug or pull on the periosteum which is intimately attached to the inner surface of the ligaments just below the epiphyseal ring. The repeated small tugs cause irritation of the periosteum which results in a gradual overgrowth of bone at the margin of the vertebral bodies. Moreover, the degenerative processes affecting the annulus fibrosus, which may manifest themselves in such a degree as to allow the formation of concentric or radiating tears or may terminate in dissolution of the annulus, eventually may permit an escape or prolapse of disc tissue which insinuates itself beneath the surrounding ligaments and augments the outward pressure upon them. In the degenerated condition of the intervertebral disc, the nucleus pulposus retains little or none of its original turgor, so that the active extruding force is furnished chiefly by muscle tone and the weight of the body borne by the vertebræ. Since the anterior longitudinal ligament is stout and strong, it tends to resist the outward pressure and, consequently, osteophytes do not commonly appear beneath it but tend to form just lateral to it where the ligamentous investments are much thinner.

Movement is apparently necessary to the development of osteophytes and when bony union of vertebræ occurs they may actually regress. If there is an associated senile kyphosis with bony union of several vertebræ, osteophytes are frequently absent in that particular segment. It should also be mentioned that osteophytes may not be prominent even in the presence of marked degeneration of the intervertebral discs, while in other cases in which degenerative changes are only minimal osteophytes may be well developed. Movement and the stresses and strains to which the joint is subjected apparently play a major rôle.

SENILE OSTEOPOROSIS. In contradistinction to other types of spinal deformity, that caused by senile osteoporosis is occasioned by changes in the spongiosa of the vertebral bodies; the whole disc system may be well preserved in spite of advanced age. Such osteoporosis probably occurs as a part of the phenomenon of senile atrophy in general, but diminished functional activity probably contributes to this atrophy. Thus, senile osteoporosis may be in part an atrophy of disuse which perhaps accounts for the lack of degenerative changes in the inter-

vertebral discs. The discs, however, all show a marked degree of expansion and are lens-shaped, the bone appearing as though melted away by the pressure of the discs. Rupture of the cartilage plates is frequent with the formation of prolapses of disc tissue in the adjacent spongiosa of the vertebral bodies, but there is little or no reaction about these prolapses. There may be in addition a degree of collapse of the rarefied spongiosa of the vertebral bodies, especially in their anterior portions. The vertebral bodies thus become narrower anteriorly than posteriorly, as well as showing an abnormal concavity of their articular surfaces due to the expansion of the intervertebral discs. The total result is the development of a kyphosis, usually most marked in the mid-dorsal region which may become extreme.⁷

BECHTEREW'S DISEASE OF THE SPINE. Bechterew's disease, Marie-Strumpell's spondylitis and spondylitis ankylopoietica are variations of the same type of spondylitis and need only be mentioned here in passing, since the intervertebral discs are only secondarily involved. The disease is in all probability the end stage of a rheumatoid type of arthritis involving the spine, and so may be infectious in origin.⁴¹ There is an extensive calcification of all the ligaments surrounding the spinal column but this occurs relatively late in the course of the disease and clinically there is immobility of the spine long before calcification of the ligaments can be demonstrated by Roentgen ray examination. The first changes are usually noticed in a narrowing of the joint spaces of the small intervertebral articulations. This is followed by complete but smooth ossification of all the ligaments, particularly the anterior longitudinal ligament, without the formation of osteophytes or bony protuberances. The spongiosa of the vertebral bodies undergoes a high degree of rarefaction, the intervertebral discs become ossified and converted into bone of the same consistency as the spongiosa and the whole spine is fused into a rigid bamboo-like column. Some degree of kyphosis is usually present.

Summary. A brief account of the development and anatomy of the vertebral column is presented with special reference to the intervertebral disc and the structures immediately surrounding it. This is followed by a consideration of the various types of pathological change which affect the intervertebral disc or its component parts. These changes form the pathological basis for the development of prolapses of disc tissue into the spongiosa of the vertebral bodies and for displacements of disc tissue in the posterior, anterior or lateral directions. Each of these is discussed in turn. Posterior extrusion of tissue of the intervertebral disc into the spinal canal is of particular importance because of the possibility of compression of the spinal cord or nerve roots. Special emphasis is placed upon the rôle of repeated minimal traumatic shocks in the etiology of the various lesions described. The review is concluded with a discussion of the effects of lesions of the intervertebral discs upon the spinal column as a whole with particular reference to the pathogenesis of adolescent kyphosis, senile kyphosis and spondylosis deformans, diseases in which primary lesions of the intervertebral discs constitute the underlying cause of the spinal deformity.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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INFECTION OF MAN WITH VIRUS OF EQUINE
ENCEPHALOMYELITIS.

A NEWLY recognized communicable disease of man is not altogether an event in these days of active investigation in the field of filtrable viruses. However, when human infections with the virus of equine encephalomyelitis were identified by Fothergill, Dingle, Farber and Connerly⁸ in the late summer of 1938, and promptly corroborated by Webster and Wright,³¹ the circumstance was of more than usual importance. The known broad distribution of the disease among animals

and the high fatality suggested a significant relationship to public health and preventive medicine. Here was another disease of animals entering into human pathology and substantiating the statement of Meyer^{17b} that as reservoirs of human disease the animal kingdom offers intriguing possibilities and surprises. The resulting complex epidemiologic problem that developed from these observations is not unexpected, in view of the generally broader pathogenicity of viruses associated with animal diseases in comparison with those whose normal habitat is man.

The agents producing inflammation of the brain include bacteria, protozoa, chemical agents such as lead, and the filtrable viruses. The infections of the brain produced by the latter group include clinical conditions known as Japanese B encephalitis,¹⁴ St. Louis encephalitis,²¹ Australian X disease,^{2,3} and now infection with the virus of equine encephalomyelitis. The viruses responsible for these four conditions are all pantropic. While they attack the central nervous system and destroy nerve cells, they also invade cells of other embryonic origin, and neurotropism is but one of several properties they possess. They are distinct from the group of strictly neurotropic viruses of which the agents of rabies, poliomyelitis and Borna disease are examples.¹³ The neurotropic viruses grow and multiply only in nerve tissues, and reach the central nervous system from peripheral sites by nerve trunks only. There is no evidence of their multiplication in the blood or transport by the blood. In general, growth in tissue culture is accomplished with greater difficulty than is true of pantropic viruses with neurotropic properties.

One other infectious encephalitis of man, the Vienna or Type A encephalitis first described by von Economo,⁶ is probably caused by a filtrable virus but this has never been proved. It differs from the four conditions in man that are known to be due to a virus, in that the seasonal prevalence is in winter and spring instead of late summer, and that Parkinsonism is a common sequela, a condition that is rarely associated with the other four diseases. The viruses of Japanese encephalitis and equine encephalomyelitis can be transmitted experimentally by mosquitoes.

The Virus of Equine Encephalomyelitis.—A subacute form of equine encephalomyelitis of horses has been known for many years in Europe as Borna disease. The cause was established as a filtrable virus in 1924.²⁰ The first recognized American epizootic of horses simulating this condition occurred in the San Joaquin Valley in California in 1930.¹⁸ There is no reason to believe that the disease was freshly introduced into the United States at this time, for similar conditions had been observed for a number of years and the Kansas-Nebraska horse plague of 1912 was probably the same disease. The identity of the infection was, however, determined by Meyer, Haring and Howitt¹⁸ when they isolated a filtrable virus from the brains of 2 horses that had died from the disease. This virus was immunologically different from that associated with Borna disease and has come to be recognized as the western variety of the virus of equine encephalomyelitis. In 1933, an epidemic of horses occurred along the Atlantic seaboard, principally in the states of New Jersey and Virginia. Ten Broeck and Merrill²⁸ identified the disease as equine encephalomyelitis and isolated the eastern type of virus, which in turn is biologically distinct from the

western type. Succeeding epidemics which have occurred east of the Appalachian Mountains have all been due to the eastern type of virus and those west of the Appalachian Mountains to the western type. The disease has been reported from a number of different countries in Europe and South America and, in all, five varieties of virus are known to be associated with the disease: the original Borna virus, the eastern and western types of American virus, and the agents associated with equine encephalomyelitis of Russia and Venezuela.

That man as well as horses might be susceptible to the virus is not a new idea. Karl Meyer,^{17a} who knows both horses and men, suspected that the unusual encephalitis contracted by 3 men working with infected horses might be due to the virus of equine encephalomyelitis. Examination of the brain of a ranch hand who died of the disease showed pathologic lesions similar to those observed in horses. The clinical impression was not proved by isolation of the virus or by the test for neutralizing antibodies in the serum of the infected persons. In August, 1938, an epizootic of considerable proportions occurred among horses in southeastern Massachusetts. In the same year 2 children died of a peculiar form of encephalitis and a local physician suggested that the disease was due to the same agent as that responsible for the prevailing epidemic among horses. From a child dying in the Children's Hospital of Boston Fothergill and his associates⁸ isolated a virus from the brain which was identified by cross-protection tests as the virus responsible for the eastern form of encephalomyelitis in horses. This observation was confirmed for the same case and for 4 others by Webster and Wright.³¹

During the same month of August, 1938, a 20-month-old child died in California. Howitt^{12b} isolated the western type of virus from the brain. It was thus established that both known American varieties of the virus could cause infection of man. Furthermore, the blood of several persons in California who had recovered from encephalomyelitis was shown to contain neutralizing antibodies for the western virus.

Encephalitis of horses had been prevalent in Minnesota during the summer of 1937. During the late summer 6 cases of human encephalitis occurred in a southwestern county of the state. Five of the patients had had contact with sick horses and all lived on farms in a region where the disease was prevalent. Two of the patients died after illnesses of 4 and 5 days' duration. The blood of another patient examined 4 months after recovery contained neutralizing antibodies.⁵ Cases of human infection have thus been substantiated in the East, the West and the Middlewest. These were all naturally acquired infections.

Fothergill, Holden and Wyckoff⁹ have recently reported the fatal infection of a laboratory worker engaged in experiments with the western type of virus. An accidental wound infection was suspected but could not be proved.

The Clinical Disease in Man.—The clinical manifestations of infection in man with equine encephalomyelitis virus differ from those of the epidemic encephalitis of von Economo in the greater severity of symptoms and the high fatality.³² In infants the onset is sudden, but in older children and adults several days of indisposition may precede active signs of encephalitis. In 2 instances the period of invasion was characterized by a remission of symptoms for a day. The first complaint of older persons is commonly of frontal headache and dizziness.

The actual symptoms of encephalitis are almost invariably abrupt and characterized by fever, irritability, drowsiness, cyanosis and convulsions. Patients are usually in a semi-comatose or comatose condition when admitted to hospital.

The course of the disease is characterized by continued tremors or muscular twitchings; rigidity of the neck is constant; and a tense anterior fontanelle is noted in infants, who likewise develop a peculiar edema about the eyes and in the upper extremities. A marked cyanosis is regular, as is deep coma. The fever is invariably high, from 102° to 104° F., with hyperpyrexia common in fatal cases. When recovery occurs, the fever drops by lysis over 4 or 5 days.

Surviving the acute stage, patients experience coma and more or less rigidity of the muscles for many days. Slow improvement with apparent return to normal is sometimes the end result, but paralyses, mental changes and other permanent residua are common. The fatality rate is high, about 60% in the Massachusetts experience. Death is commonly due to encephalitis, with terminal evidence of myocardial insufficiency or pulmonary symptoms contributing little as actual causes of death.

Clinical recognition of the disease depends upon the occurrence of a peculiar type of human encephalitis in association with a recognized epidemic among horses, on the clinical course of the disease and on laboratory examination of the cerebrospinal fluid. The virus has been isolated from the blood of infected horses but is known to be present for an extremely short time. It has not been isolated from the blood of humans. The blood serum, however, contains neutralizing antibodies at death and they tend to appear early and promptly, within 6 to 8 days. In continuing illnesses Fothergill has suggested this test as an aid in diagnosis.²² The cerebrospinal fluid is under increased pressure and may contain from 200 to 2000 cells of which 60 to 90% are neutrophils. The blood shows a well-marked response of neutrophilic cells.

The pathologic changes associated with the disease in man are described by Wesselhoef, Smith and Branch³² as consisting of a profound, acute, disseminate and focal encephalomyelitis characterized by intense vascular engorgement, perivascular and parenchymatous cellular infiltration and extreme degenerative changes in the nerve cells. The gross pathologic manifestations are not specific. In the severe cases the microscopic reaction can readily be distinguished from any of the common types of encephalitis.

Epidemiology.—Infection with the virus of equine encephalomyelitis was first recognized as a disease of horses, but there is some doubt whether it is primarily a disease of these animals. Certainly it is widespread among horses and mules and its economic importance has been recognized for several years. An idea of the frequency of encephalitis among horses is obtained from the reports of the United States Department of Agriculture¹⁹ and from the data of Shahan, Giltner and Schoening.²⁶ Since reporting of human disease is far from complete, the available information for diseases of animals is probably still less reliable. At any rate, somewhat more than 23,000 horses are known to have contracted the disease in the United States in 1935; in 1936, some 4000; in 1937, 170,000; and in 1938, about 184,000. It was reported from 39 states in 1938. Whether infected with the eastern or western variety

of the virus, the symptoms presented by horses are much the same. The differences in case fatality are rather distinct, as judged by the results for 1938, when the rate for horses infected with the western variety was about 25% and with the eastern virus in excess of 95%. The severity of the western disease varies considerably from year to year and sometimes the fatality is as great as 50%. In general, it remains much less fatal than the eastern disease. The seasonal prevalence is rather sharply limited to summer and early autumn. The distribution of cases in infected areas is always scattered, and there is no evidence of contact infection.

The wide geographic distribution of the disease in humans is shown by the proved cases that have occurred in Massachusetts, Minnesota and California. The only known epidemic of human infection is that reported by Feemster⁷ in southeastern Massachusetts during the summer of 1938. Epidemics among horses had occurred for a number of years in mid-Atlantic coastal states but previously had not been recognized in New England. The Massachusetts outbreak among horses began about the middle of July in areas near the Atlantic coast. The peak of the outbreak was reached during the week ending August 27, and thereafter rapidly declined. In all, some 250 horses were reported as infected and more than 90% died. The outbreak was established as equine encephalitis by isolation from the brains of 6 horses of a virus which corresponded to the eastern type described by Ten Broeck and Merrill.²⁸ The prevalence of mosquitoes that summer had been unusually great. The first human cases likewise occurred in August. The epidemic curve for human cases paralleled that of the horse epidemic. Total cases reported for humans numbered about 40. The exact number remains indefinite because of inadequacies in information about some few of the 45 suspected cases that were reported during the outbreak. The clinical diagnosis was confirmed for 21, either by isolation of the virus or by demonstration of neutralizing antibodies. A significant observation was the fact that few of the people who developed the disease had had any contact with horses, and there were no multiple cases in families. A good two-thirds of the cases involved infants and young children less than 10 years of age. The oldest patient was aged 55. The distribution among the sexes was even. The fatality rate in the Massachusetts outbreak was about 60%. Should an epidemic due to the western virus occur among humans it would be expected, on the basis of experience with the disease in horses, that the attack rate would be greater and the fatality less.

Much evidence exists that this infection is not limited to horses and to man. In 1933 Giltner and Shahan¹⁰ produced the disease experimentally in pigeons and at that time suggested that birds might have a part in the transmission of the disease in Nature. Subsequently Remlinger and Bailly²⁴ showed that a wide variety of birds were susceptible to the virus, as well as the several laboratory animals that had been used in the study of the virus since it was originally isolated. In September, 1938, numerous pheasants and other wild birds were found dead or in a helpless paralytic condition in certain rural sections of Connecticut. Four moribund ring-necked pheasants were examined by Tyzzer, Sellards and Bennett³⁰ and found infected with the eastern variety of equine encephalomyelitis virus. Later they demonstrated that quail and domestic fowl could be infected with the virus

isolated from pheasants. With the demonstration of infection among birds in Nature the original observations on susceptibility took on new significance. Migratory birds clearly were implicated in the epidemiology of the disease.

Whatever may be the primary animal reservoir of the disease, the epidemiologic characteristics of the disease suggest the activity of some insect in transmission from host to host. Kelser¹⁵ in 1933 had allowed the tropical *Aedes ægypti* to feed on guinea-pigs infected with encephalomyelitis virus. Six to 8 days later they were transferred to normal guinea-pigs and these animals died of the typical disease. This proved that the virus could be transmitted by mosquitoes, but greater epidemiologic significance was given the fact when Merrill, Lacaille and Ten-Broeck¹⁶ succeeded in transmitting the virus by the native mosquitoes of the area where equine encephalomyelitis had occurred among horses. They also showed that the cases among horses corresponded in distribution with the range of the mosquitoes. It was thus apparent that mosquitoes must be given important consideration as vectors. Subsequently, encephalomyelitis virus has been transmitted to laboratory animals by at least 6 species. However, the presence of the virus in the blood of horses is distinctly transitory and if the disease is transmitted by mosquitoes it is almost essential to postulate some other animal reservoir.

The studies of Syverton and Berry²⁷ have shown that another insect, the tick *Dermacentor andersoni*, can transmit the western type of virus and likewise pass it on to succeeding generations of insects through the ova.

The well-marked susceptibility of mice to nasal instillation of the virus suggests that small rodents may be concerned in the natural transmission of the disease, and Syverton and Berry²⁷ have shown that at least one wild rodent, the gopher *Citellus richardsonii* (Sabine), can be infected by instilling the virus into the nose.

The evidence presented suggests that direct contact infection plays no part in the natural transmission of the disease to man or to the horse. Multiple cases on the same farm are rarely observed in epizootics among horses. More than one human infection has never been observed in the same family. The natural reservoir of the virus is not known. It rather definitely is not man. No chronic cases have been observed and no human carriers have been found. Furthermore, the virus is present in the blood a very short time. It would seem just as certain that the horse is not the natural source of the virus. The high fatality among horses of itself is against survival of the virus in that species. Much the same epidemiologic considerations apply for the horse as for man. The probable source is more likely some animal species where the virus has more general distribution than in man or in horse and where the natural susceptibility is of an order that produces a more balanced equilibrium of infection and resistance, with a resultant widespread incidence and low fatality. The demonstration of the virus among birds in Nature has great importance. The rapid development of epidemics among horses is compatible with the conception of birds as a reservoir. Tyzzer, Sellards and Bennett³⁰ believe that the term equine encephalomyelitis is misleading and that the disease is actually a primary infection of birds; and that under accidental circumstances or when infection in Nature attains a certain level that transmission

to horse and to man is possible, both being accidental and secondary hosts. Small, wild rodents demand consideration. Whatever the actual reservoir of infection, insect transmission is strongly suggested by the scattered distribution in epidemics of both horse and man, and by the striking seasonal distribution. Experimentally, transmission of equine encephalomyelitis virus is possible by ticks and by a number of mosquitoes. Evidence is still lacking that this occurs in Nature. The mechanism by which infection is carried over from season to season is also unknown. Migratory birds, infection in rodents, and hibernating ticks offer possibilities.

Prevention and Control. No sound program for prevention and control is possible with the knowledge available. Effort should be directed toward limiting the disease in horses and mules. At least this is one known reservoir, but not too important if mosquitoes are the active vectors, because of the short time the virus is in the blood. A practical method of control is available in active vaccination. An attenuated active virus was first used for the immunization of horses^{12a, 23, 29} in 1934. That method is not wholly satisfactory if transmission of the disease is by insects because of the circulation of active virus in the blood of inoculated animals. An advance was made when Shahan and Giltner²⁵ produced active immunity in horses by injections of infected brain inactivated by treatment with formalin. Their satisfactory results were confirmed by Cox and Olitsky⁴ and the preparation became rather widely used. The improved vaccine now used has infected embryonic chick tissue as the source of virus for the vaccine. The development of this biologic product is based on well-controlled experiments.^{1, 11} As a method of vaccinating horses and mules it has proved more effective than vaccines made from brain emulsion. Most of the widespread vaccination of horses during the 1938 epidemic was by this method. The duration of the immunity produced remains undetermined.

Individual measures for the protection of man are best directed toward the presumed insect vector of the disease. The screening of houses in infected areas is advisable and children should not be permitted out of doors after sun-down, a lesson learned from the epidemiology of the disease in horses where night pasturing has been found of particular danger, presumably because of the activities of mosquitoes then. Vaccination of man is not advised except under particular circumstances associated with occupation. Vaccination on a large scale would never be indicated because of the low incidence in man. Isolation and quarantine have no place in the control of the human disease. Much can be accomplished by the attitude of physicians toward unusual cases of suspected poliomyelitis or encephalitis, occurring during the months of seasonal prevalence of equine encephalomyelitis, and particularly if the disease is currently epidemic among horses.

The public health problem that has developed from these observations is of more importance than indicated by the few sporadic cases and the one small outbreak that have been reported in man. The virus is known to be distributed throughout a goodly part of this country. With adequate observation the extent and number of reported cases in man will probably be much increased. Meanwhile, studies in relation to a possible insect vector and the principal reservoir of infection are under way.

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ORIGINAL ARTICLES.

ISLET CELL TUMORS OF THE PANCREAS.*

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IN 1927, Wilder,⁹ with others, reported the case history of a physician who noted sudden attacks of weakness, faintness and paraesthesia, progressively increasing in severity and causing trembling and profuse sweating. The attacks were controlled by carbohydrate administration, but soon it became necessary to feed him even while asleep. Metabolic studies disclosed hypoglycemia and at operation, resorted to in the hope of providing relief, a tumor of the pancreas with metastases in the liver was discovered. At pathologic examination this was shown to be a malignant islet cell tumor and insulin was found in a liver metastasis. This brilliant diagnosis from complete clinical and pathologic studies firmly established the disease hyperinsulinism which had been postulated by Seale Harris¹ in 1923 and subsequently supported by reports of its minor forms. Previously some 20 cases of islet cell tumor, diagnosed pathologically, had been reported but no clinical correlation had been established. More recent investigations show an incidence of such tumors in 1 of 800 or 1000 autopsies, but related symptoms have been described in only 20% of these cases.

* Read before the Association of American Physicians, held at Atlantic City, N. J., May, 1939.

In the year following Wilder's report, McClenahan and Norris,³ and Thalhimer and Murphy⁵ described somewhat similar symptoms in patients who, at autopsy, were found to have an islet cell tumor of the pancreas, and some months later we² had the opportunity to study such a case and to remove an islet cell carcinoma with entire and permanent relief of symptoms. Since that time the number of cases recognized and successfully treated or identified at necropsy has grown to somewhat less than 100. The most extensive series is that of Whipple⁷ who has reported 11 cases; most publications concern individual cases. The subject has been carefully reviewed by Sigwald⁴ in France, by Wauchope⁶ in England and by Whipple,⁸ Womack¹⁰ and others in America.

In our first report it was necessary to leave in abeyance the question of cure since the tumor possessed characteristics of malignancy and, though careful search did not disclose any metastases, it could not be definitely asserted that they would not later make their appearance. Now, more than 10 years later, the patient is in good health and without any evidence that metastatic tumors, such as occurred in Wilder's and other cases, have developed. It should also be said that this patient has remained free of any disability related to the uncontrolled over-production of insulin for which she was treated by surgical operation. In each of these respects, then, it seems reasonable to assume a cure of the condition. In the intervening time, among other cases of spontaneous hyperglycemia encountered, we have been able to study 3 additional patients from whom an islet cell tumor has been removed as well as a patient with persistent and severe diffuse hyperinsulinism who has obtained complete relief from her disability for a period of 10 months following resection of a large part of the pancreas. These cases will be reported briefly here.

Case Reports. CASE 1.—A female, aged 52 complained of exhaustion in September, 1922, then feeling ill she threw herself on the bed and gradually became comatose. She was restless, tossed about, grimaced and failed to comprehend questions. Sweating and vomiting occurred. Consciousness returned in an hour but the feeling of exhaustion persisted. Similar attacks were experienced 6 times within the next 2 years and from then on they increased in duration, frequency and severity. After it was noted that food would abort an attack, frequent lunches were adopted as regular treatment but later they seemed to lose their effect. Attacks became more frequent and the comatose state more prolonged; convulsions, incontinence and temporary hemiplegia sometimes occurred.

The patient's general physical condition was not abnormal except for her carbohydrate metabolism. During an attack blood sugars were at severe hypoglycemic levels. A blood sugar tolerance curve was of the diabetic type, but excessive amounts of sugar usually provoked hypoglycemia. Epinephrin caused hyperglycemia. Varying the rate and amount of carbohydrate intake permitted production and some restraint of symptoms, but proved to be an unreliable and erratic mode of control. Continued frequent dosage with small amounts of carbohydrate by mouth would keep the patient in a normal condition for considerable periods but, on the other hand, the

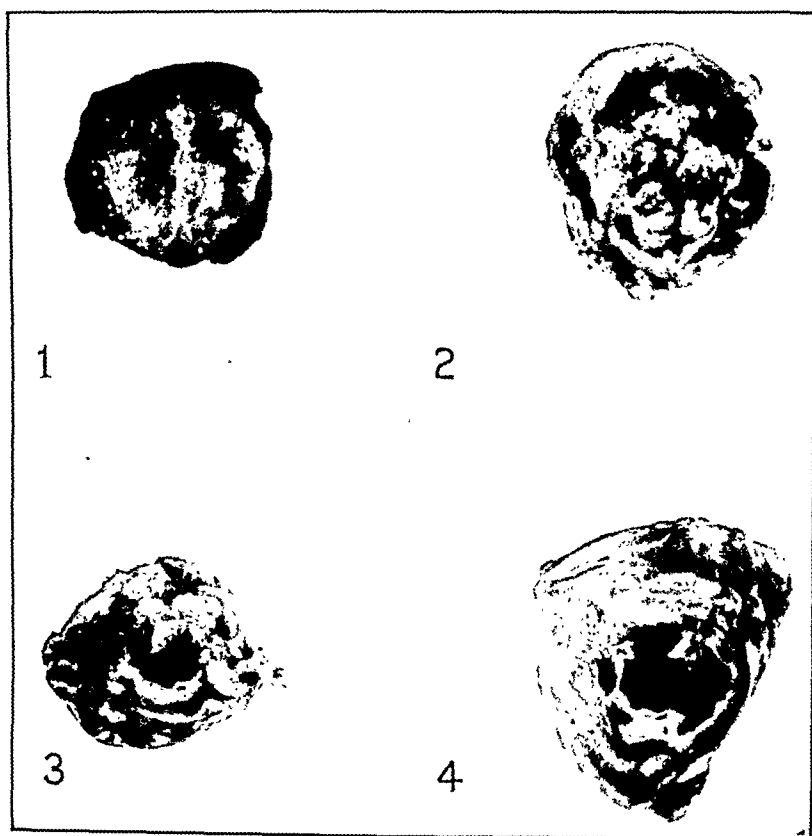


FIG. 1.—Four islet cell tumors. Gross appearance, showing relative size.

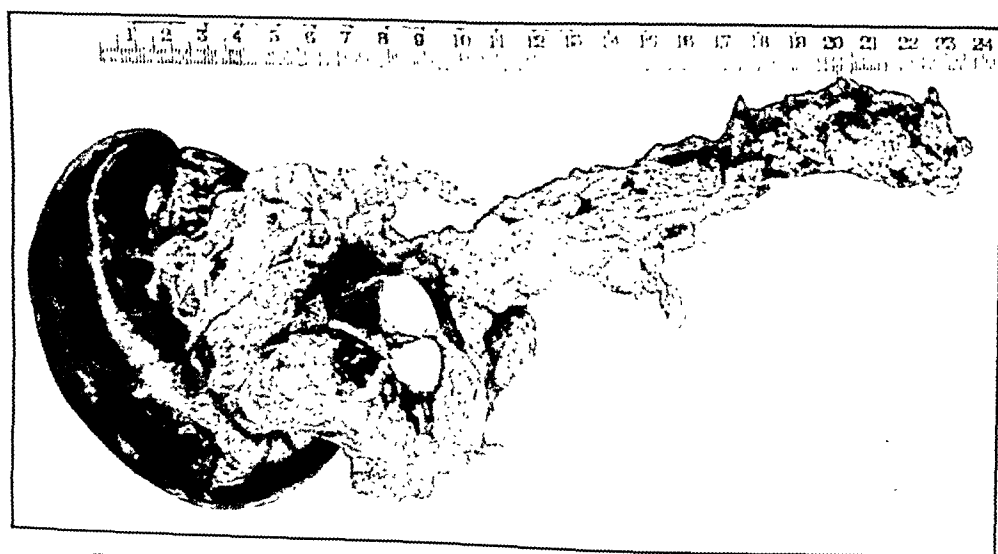


FIG. 2.—Case 4.—The islet tumor *in situ*, sectioned and turned back. Note the grayish-white color of the growth in contrast to the normal surrounding pancreatic tissue.

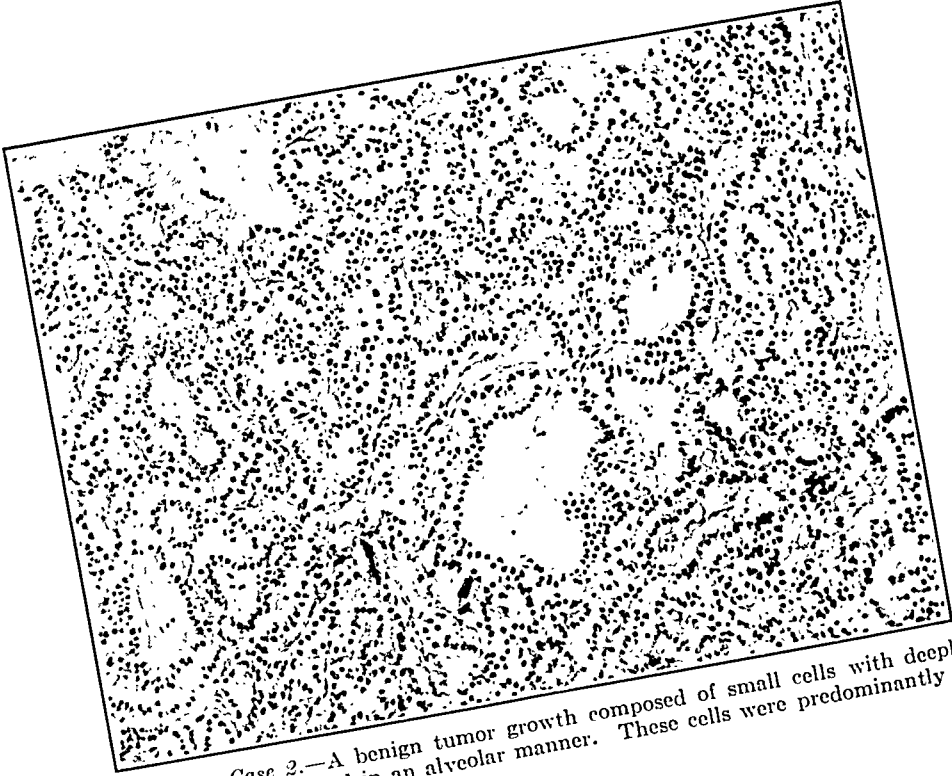


FIG. 3.—Case 2.—A benign tumor growth composed of small cells with deeply stained nuclei arranged in an alveolar manner. These cells were predominantly of the Alpha type. ($\times 75$)

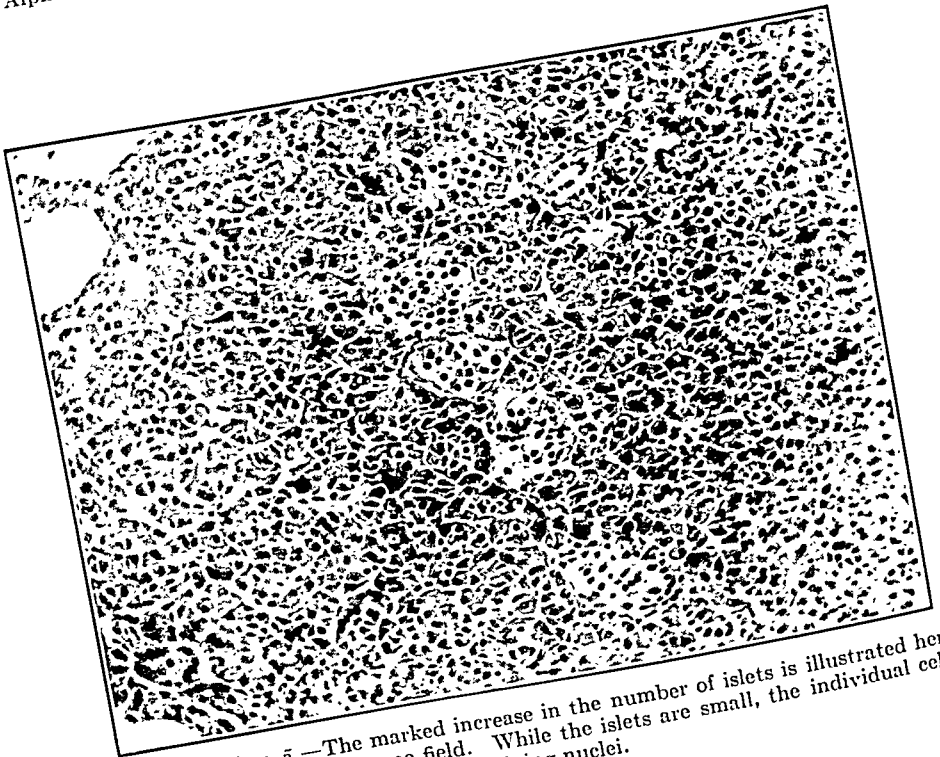


FIG. 4.—Case 5.—The marked increase in the number of islets is illustrated here by the presence of five in one field. While the islets are small, the individual cells are hypertrophied and have deeply staining nuclei.

dose of carbohydrate administered to cure one attack sometimes appeared to provoke another. With Wilder's case in mind, operation was advised and one of us removed an islet cell tumor from the body of the pancreas. A fibrous pseudo-capsule, invaded in places by tumor tissue, separated the normal-appearing surrounding pancreas from the tumor mass which showed large cells arranged in cords and in masses with little stroma. The nuclei varied considerably in size. Using special stains, granules of the Beta cell type were demonstrated in 20% of the cells; in most of the remaining cells both types of granules appeared in the same cell. In some places, pancreatic ducts were found embedded in a dense fibrous connective tissue stroma. Through the kind coöperation of Prof. Best, Dr. D. A. Scott analyzed this and also specimens obtained from later cases. Insulin was found but, in this case, the examination was not quantitative since his present method for determining insulin in small quantities had not been developed.

CASE 2.—A woman, aged 25, in the third month of pregnancy (April, 1934), had 5 epileptiform attacks in 3 days, mostly in the early hours of the morning. The seizures were characterized by muscle twitchings, incoördinate movements and loss of consciousness. Twenty-eight days after confinement the patient experienced another attack similar in character but with numbness in lips, hands and feet, extreme weakness and vertigo at onset. For a time, attacks occurred daily; later, they became less frequent. She could not be roused for the 2 A.M. or 6 A.M. feeding of the baby. Some improvement was noted with administration of ephedrine but this soon ceased to be effective. The baby was weaned and following this the patient had fewer attacks for some time. With each menstrual period, however, attacks recurred and, besides the more severe ones, there were periods when numbness of the lips interfered with speech, when she became drowsy, clumsy or "lazy," and showed lack of interest and emotional blunting.

The patient was admitted to hospital on July 30, 1935. A series of generalized convulsions occurred at about 5 A.M. on August 1 and succeeding days. Blood sugar levels during these attacks were usually around 0.04%. Delaying food provoked attacks and complete relief was obtained by glucose administration. A blood sugar tolerance test was of the diabetic type, with marked glycosuria. A general physical examination revealed nothing of importance save a moderate reduction in weight. On Roentgen-ray examination the skull was normal.

The introduction of carbohydrate meals at 11 P.M. and 4 A.M. appeared to control the attacks for a time but gradually became less effective. Operation was advised and undertaken. After careful search and no tumor found, a resection of all the pancreas to the left of the inferior mesenteric artery was carried out. The excised pancreas showed hyperplastic islands and four times the normal insulin content. From a surgical standpoint the patient made a good recovery; no attacks appeared in the 15 days following operation. This period of freedom from attacks, we now believe, was due to the post-operative diet which was rather high in carbohydrates. Attacks of marked severity then occurred and some considerable study of various dietary regimens led us to prescribe a diet with added carbohydrate to cover the probable periods of hypoglycemia. On this diet the patient remained relatively free of attacks, but because of an increase of 90 pounds in weight she attempted to diminish her diet; the attacks recurred and the patient returned to our care in January, 1938. In view of the possibility that a tumor had remained undiscovered at the first operation, it seemed advisable to re-explore the pancreas. After mobilizing the second portion of the duodenum, a tumor was palpated in the head of the pancreas and removed with some little difficulty because of hemorrhage. The tumor tissue consisted of small cells with deeply stained nuclei arranged in cords and alveoli. A majority of the cells contained granules of the Alpha type, and

the insulin content was found to be approximately 8 times that of normal pancreatic tissue. Under dietary restriction the patient lost her excess weight; blood sugar tolerance tests gradually became normal and she has been on ordinary diet for the past year. During the 20 months following the second operation she has felt well and there has been no evidence of recurrence of hypoglycemia.

CASE 3.—A woman, aged 47, 3 days following parturition in 1934, had numbness about the mouth for 3 days. It then became more widespread, with mental confusion and loss of memory. In August, 1935, she had generalized convulsions and by March, 1936, similar attacks occurred almost daily, but ceased during pregnancy—May to July, 1936. Miscarriage occurred and the attacks returned. In a later pregnancy, there were only two such episodes until the ninth month when a severe convulsive seizure occurred, lasting 8 hours. Pregnancy was terminated and daily attacks followed.

The patient was brought to hospital unconscious, *in status epilepticus*. Her health otherwise had been good but her husband had noted an increasing mental dullness and emotional instability. There was a moderate sized colloid goiter, otherwise the physical examination revealed nothing abnormal except during the convulsive periods when opisthotonus, spasticity, increased reflexes and bilateral Babinski phenomenon occurred. The blood sugar was .033%. Glucose given intravenously stopped the convulsions; the patient opened her eyes, followed a light and seemed to understand but could not speak. In an hour, she answered questions slowly and inarticulately and obeyed commands. The following day she had several seizures which were relieved by glucose. The next day a glucose tolerance test showed notably low values throughout. It seemed impossible to raise the blood sugar above the normal level by glucose given simultaneously by the intravenous route and by duodenal drip, so further investigation was abandoned and operation advised.

At operation, which was carried out under a spinal anesthetic, a tumor was palpated deep in the head of the pancreas and excised. The change was dramatic. In 15 minutes following the removal of the tumor the patient roused and attempted to speak. Her pale, clammy skin dried and breathing became normal.

The tumor was made up of cells, some of which had a clear cytoplasm, others having fine granules. The nuclei, for the most part, were small and deeply stained. Using Bowie's stain, some 80% of the cells showed granules of the Beta type. The insulin content of the tumor was 85 units per gm., about 40 times the amount found in normal human pancreatic tissue.

Following operation the patient seemed to improve temporarily. The blood sugar level remained continuously in the normal zone, and a blood sugar tolerance test was nearly normal. However, she gradually became more confused mentally, more restless (required sedation), ceased to recognize people, lost any understandable speech, and developed increased reflexes, muscle wasting, aphasia and incoördination. Measures of reëducation were undertaken and gradual improvement has taken place over the last 15 months but she is still unstable emotionally, irritable, her memory is poor, and dysarthria is quite marked. She has gained in weight, the muscle wasting in the hands is much improved, but coördination is not good. She feeds herself with difficulty, is unable to walk without assistance and requires help with dressing. Fasting blood sugar levels, as well as the blood sugar tolerance test, are now normal. There have been no further hypoglycemic attacks.

CASE 4.—This patient is a woman, aged 46. It is possible that the first symptoms of her illness occurred 8 years ago, when it was noticed that she was somewhat irritable, became hysterical in behavior, then moody and,

subsequently, remembered little of her actions. She was well apparently for 2 years; then these symptoms recurred. Within a short period she had several attacks which were recognized as hypoglycemic in origin and carbohydrate was prescribed for their relief. Though this treatment was satisfactory for a time, her friends noticed that she became careless in dress, speech and behavior and antagonized people by her comments and actions. It is not improbable that many of these incidents took place while she was in an unrecognized state of mild hypoglycemia, but it seems certain that there was considerable alteration in character apart from the attacks. She felt moody, sullen and irritable most of the time. At first there was a gradual, then a rapid increase in the frequency and severity of the attacks until it became necessary to administer 20 gm. of glucose every hour and a half during the day, in addition to meals, and every 2 hours during the night to prevent unconsciousness. On this routine she became extremely obese and applied for relief because of this, as well as because of the increasing severity of her attacks.

The patient was admitted to hospital and, in spite of 45 gm. of glucose administered at 12, 2,30 and 5 A.M., respectively, a 7.30 A.M. estimation of blood sugar was .037%. This rose in 30 minutes, after administration of 100 gm. of glucose, to .075% and in 2 hours had gradually reached .090%, from which point it declined until at 4.30 P.M. it was .040% and definite signs of hypoglycemic reaction were present. Her general physical condition was normal except for the obesity. The sella turcica was normal. The metabolic rate shortly after sugar administration was +12%. On examination, urine and blood were normal.

Operation was advised and undertaken but was difficult on account of the amount of fat surrounding the organs. A tumor was found in the tail of the pancreas, but splenectomy and partial resection of the pancreas were necessary. Though febrile following operation, the patient felt well apart from a sensation of distention of the abdomen. The blood sugar came down to normal when the intravenous glucose was discontinued. On the third day her temperature rose suddenly to 107° F., accompanied by a corresponding rise in pulse and respiratory rate and she died in 3 hours. We were unable to discover the cause of the sudden hyperthermia and necropsy was not permitted. Ziskind¹² has recorded a similar case.

The tumor weighed 3.4 gm. and was enclosed in a definite capsule. It consisted of rounded and cord-like masses of cells with a granular cytoplasm, 98% of which showed Beta granules. The adjacent pancreatic tissue removed with the tumor showed a great increase in the number and size of islets. The insulin content of the pancreas was 1.9 units per gm. of tissue, while that of the tumor was 4 times as great.

CASE 5.—A woman, aged 22, was kindly referred by Dr. E. F. Brooks of St. Michael's Hospital. This patient was well until February, 1935, when, following an attack of influenza, jaundice occurred and, with recovery, she commenced to complain of excessive fatigue. Great exhaustion followed mild exercise. In June, 1936, she had a convulsion in a motor car. A short time later, her parents, returning home, found her unconscious. She had probably been so for 8 hours when her physician arrived and, suspecting a hypoglycemic state, administered glucose; she regained consciousness in 10 minutes. Such episodes were repeated whenever she went too long without food or indulged in any exercise. On several occasions blood sugars were found to be 0.02 to 0.03%. Provoked attacks gave similar values. A glucose tolerance test was of the diabetic type. Diet proved ineffective in controlling the attacks of hypoglycemia and operation was recommended.

On November 14, 1938, the pancreas was carefully examined but no evidence of tumor was revealed. As other possible causes of the hypoglycemia could reasonably be ruled out, a resection of 34 gm. of the pancreas was

carried out, leaving a mass of pancreatic tissue of approximately 1 by 2 cm. Though the patient later developed an empyema requiring drainage in February, 1939, she has remained free of all attacks; numerous blood sugar estimations all have been within normal limits during the 10 months since operation, and no glycosuria has occurred on normal diets.

Though no tumor was found in this case, there were large numbers of islets in the pancreas (5 per low power field), which were made up of very large cells with deeply-staining nuclei. This probably explains the hyperinsulinism. The insulin content of the tissue was normal.

TABLE 1.—CASES OF HYPERINSULINISM.

Case.	Tumor.			Insulin content units per gm.	Cell type.	Result of operation.
	Color.	Weight gm.	Position.			
1	Red	0.84	Body	+	20 per cent β cells; remainder contained granules of both types. (Malignancy.)	Cured
2	A. Yellow pink	20.0	Tail	8	Hyperplastic islands.	Unimproved
	B. Maroon	2.25	Head	17	Majority α cells.	Cured
3	Maroon	1.3	Head	85	80 per cent β cells.	Cured
4	A. Yellow red	36.0	Tail	1.9	Increased number and size of islets of normal pancreas.	Cured (Died)
	B. Maroon	3.4	Tail	8	98 per cent β cells tending to infiltrate pancreas.	
5	Yellow pink	34.0	Tail	2	No tumor found. Islet tissue increased due to increase in islets but more to hypertrophy of individual cells.	

A—Pancreatic tissue.

B—Tumor tissue.

A normal pancreas weighs 60–100 gm., its islet tissue $1\frac{1}{2}\%$ of this. Alpha and beta cells are approximately equal in number. The insulin content of the pancreas is 2 to 3 units per gram.

Discussion. Some of the salient facts in regard to these cases are collected in Table 1. Cases 1 and 2 appear to be cured. It seems important to remember that, though hyperplastic islands and increased insulin content of the pancreas may be present, their reduction by resection of a large portion of the pancreas may not provide a cure, as is illustrated in Case 2, though the happy outcome in Case 5, up to the present at least, provides some hope that this may take place, providing a sufficient volume of the pancreas is removed. Though many resections reported in the literature have been relatively unsuccessful, there are a few which have been followed by complete relief of symptoms; in most of the failures one suspects the removal of insufficient pancreatic tissue. But, even though marked hyperplasia be demonstrated, there can be no guarantee that a concealed tumor may not be the principal cause of

hyperinsulinism, as is illustrated in Case 2. In earlier reported cases re-operation has also proved successful in locating a tumor previously overlooked. The discovery of multiple adenomata in some cases makes it advisable to perform a second operation in any case which does not show a restoration of the carbohydrate metabolism to normal following the removal of an islet cell tumor. The necessary surgical procedures vary in the individual case. Since the tumor mass is small and may be entirely surrounded by normal pancreas, as it was in 2 of our cases, vision alone cannot be relied upon to locate it. Complete mobilization of the pancreas to permit adequate palpation is the absolute essential of the technical maneuver and, if the patient is obese, even then its discovery may not be easy. The mobilization must permit palpation between thumb and fingers of the head, body and tail of the pancreas. This is accomplished by dividing the peritoneum on the concavity and convexity of the first and second part of the duodenum. One can thus displace the head of the pancreas from under the mesenteric vessels and thoroughly palpate the whole structure. By dividing the peritoneum along the inferior border of the body and tail of the pancreas, this area may also be thoroughly palpated between the thumb and fingers.

In Case 3, the severe degree of damage sustained by the nervous system, as evidenced by incoördination of voluntary effort as well as by a changed mentality, as a result of the prolonged activity of the islet cell tumor, and the astonishing concentration of insulin in the tumor are worthy of note. Recovery from the injury is still progressing. The fourth case illustrates those alterations in character and mental outlook which are likewise causing concern in some of our unstable diabetics of long standing whose reactions to a certain dose of insulin are erratic and unpredictable. The obesity dependent upon increased carbohydrate intake complicates necessary surgical procedures.

In Case 5, an increased number of islets in the pancreas together with a hypertrophy of the individual cells, rather than an encapsulated tumor, appears to be the cause of a severe hyperinsulinism since, with resection of all but a portion of the pancreas measuring only 1 by 2 cm., a complete cessation of all symptoms occurred and has persisted for 10 months. This does not necessarily imply permanent cure any more than resection of a hyperactive goiter is always followed by permanent cure, nor is it entirely impossible that an overlooked adenoma may some day cause an explosion. However, isolated, severe attacks have seldom, if ever, occurred when the condition has become well established. The lapse of 10 months without any recurrence strongly suggests that the condition is adequately controlled.

Dietary regimens of various kinds have been tried in these cases. In our hands they have proved ineffective in controlling for long

the symptoms of severe hyperinsulinism. As 4 of our patients had islet cell tumors, perhaps this is not surprising. Better results might have been obtained in milder cases dependent upon a diffuse hyperplasia of islet cells.

Anterior lobe hypophyseal extracts of considerable effectiveness can now be obtained and some have even been tried in tumor cases. The effect of these extracts in animals has been shown to be exerted on the cells of normal islets. Unless a specific effect on tumor cells can be demonstrated, it might seem preferable to avoid such treatment in tumor cases, since there is little likelihood of affecting the tumor cells without at the same time destroying the normal insulin-producing units and thus producing diabetes plus erratic insulin release from the tumor cells. If a means of accurate clinical differentiation of the diffuse islet cell hyperplasia and the localized tumor mass could be devised, operation for the latter group and relative impairment of the islet tissue by hypophyseal extracts for the former might seem to be logical. But, as Dr. Young¹¹ has kindly pointed out, hypophyseal extracts operate on an all-or-none principle, insufficiently injured cells reverting to normal in a few days.

The insulin content of a normal human pancreas is approximately 150 units, or 6 mg. The actual production of insulin per day is much more difficult to determine and probably is dependent on the amount and composition of the diet, the antagonistic balance with other hormones, as well as on numerous other factors. Of much importance, however, is the delicate balance which is normally maintained between these various factors to permit of a normal concentration of sugar in the blood and tissues. In the presence of islet cell tumors both of these mechanisms are disturbed. The islet cells of tumors exceed the normal islet tissue of the whole human pancreas by one to four times and approximate that found in the principal islets of fishes. Regulation of insulin production and release may be disturbed by excessive production and continuous or erratic excessive release of insulin from these tumors which probably are not under the same measure of control as the normal islet tissue. In fact, the histories of these patients indicate that all of these factors may operate together or separately. The actual concentration of insulin found in the tumors is not to be regarded as an adequate measure of their activity, though it is interesting to note that it ranges between 4 and 40 times that of normal pancreas and nevertheless, in amount, is not equal to that of a normal pancreas. It should be stated that these values are applicable to the time of excision only, are not necessarily either maximal or minimal, and are not to be compared with concentrations found in normal tissue which may vary but within much narrower limits. The range of variation may depend upon differences in rate of production or storage or secretion, or a balance between these. On this account,

the amount of islet tumor tissue, the cell type and the insulin content of the tumor can only be related in a general way to the clinical expression of insulin overdosage. As they collaborate in varying degrees in releasing a noxious agent into the body, great differences may be expected in the symptomatology at various times, with but one feature in common—the general tendency to increase in severity as time passes.

Besides its dominant rôle in the production of symptoms of hyperinsulinism and excess insulin administration, hypoglycemia may be found playing a secondary, even an incidental rôle, in numerous other conditions. Among these, liver disturbances—tumor, atrophy, fatty infiltration, and poisoning caused by chloroform, phosphorus, arsenic or alcohol—and muscular dystrophy are associated with impaired glycogen metabolism; extreme fatigue and infections with excessive use of the available carbohydrate; lactation, pregnancy and renal glycosuria with abnormal drainage of the blood sugar; while a loss or damage to the normal antagonists, such as occurs in diseases of the thyroid, adrenal cortex and pituitary gland, accounts for another group of hypoglycemias. Imperfect adaptation to diet or perhaps some hyperactivity of the islet cells, particularly in children, may give rise to a condition of functional hyperinsulinism which is readily controllable by dietetic measures.

A study of the associated clinical symptoms in such cases will usually provide adequate differentiation. The past history of a case of islet cell tumor is one of minor attacks of exhaustion or fatigue followed by isolated episodes of more severe nature in which many of the well known symptoms of insulin overdosage may appear up to the stages of acute mania, unconsciousness or convulsions. Increasing frequency of attacks, together with the volunteered statement that ingestion of food relieves or totally inhibits an attack and a consequent development of obesity characterize the later course of the disease.

Signs of degeneration of the nervous system, analogous to those found in experimental insulin overdosage in animals, may appear relatively early and be accompanied by irritability, emotional instability, a loss of the finer attributes of character and reversion to vulgarity. Carelessness in speech, dress and deportment accompany these manifestations and, in later stages, may become irreversible characteristics. These developments, together with the technical difficulties incident upon obesity, make early diagnosis and removal of tumors desirable.

In attacks, the blood sugar is invariably low; repeated examinations to confirm this are necessary. There is a greater tendency for the attacks to occur a long time after food—in the early morning hours—or after exercise, and attacks may be provoked by deprivation of food or by the administration of small doses (5 units) of

insulin. It may be difficult to raise the blood sugar with glucose, or too much glucose may initiate another attack. In many cases the blood sugar tolerance test may be of the diabetic type. Dietary treatment may suffice for the milder cases of diffuse hyperplasia of islet cells, but it is doubtful if it has ever been effective for long in tumor cases.

The number of cases of true hyperinsulinism discovered in the past 10 years bears little relation to the incidence of islet cell tumors found at autopsy by careful examination. While it is true that in many instances such tumors need not be expected to produce well marked clinical symptoms, it also seems likely that careful review of patients suffering from nervous or mental disabilities, with islet cell tumor in mind, would yield a much larger harvest of these cases.

Summary. Four cases of islet cell tumor of the pancreas and one case of diffuse hyperplasia of islets with hypertrophy of islet cells are presented.

A varied clinical symptomatology, dependent on the hypoglycemia is shown, which parallels the results of experimental hyperinsulinism in animals. From the mildest of isolated episodes, the attacks run a course eventually resulting in marked mental deterioration and degeneration of the nervous system; marked obesity occurs as the disease progresses. Thus, early diagnosis and adequate treatment are especially desirable, not only to prevent the unfavorable later results but also to avoid the increased technical difficulties encountered in late operation. While, in mild diffuse hyperinsulinism, dietary treatment may suffice and the patient revert to normal, the process in tumor cases is progressive and nothing short of excision of the tumor will give the patient relief from his symptoms. The islet cells in these tumors exceed the mass of islet cells in the normal pancreas, and their insulin content is from 4 to 40 times that of the normal pancreas per gram, but not *in toto*. The clinical symptoms seem largely dependent upon uncontrolled secretory activity of the tumor rather than upon continuous production of excess quantities of insulin, until the later stages when the latter factor plays a larger rôle.

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SHOULD DIGITALIS BE ADMINISTERED TO PATIENTS WITH PREEXISTING PARTIAL HEART BLOCK?*

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THE orderly transmission of impulses from the auricles to the ventricles may be delayed, may be occasionally blocked, or may be blocked completely. In the latter event, when no impulses pass from auricles to ventricles, auriculoventricular dissociation is said to be present and the term "complete heart block" is applied. Any defect in auriculoventricular conduction short of complete dissociation is called partial heart block.²⁵

Mackenzie¹⁷ and Cohn^{5,6} demonstrated many years ago that digitalis may produce an effect on auriculoventricular conduction, varying from simple lengthening of the a-c or P-R interval to complete block. In the absence of medication, these conduction defects also are observed not uncommonly in patients with rheumatic or arteriosclerotic heart disease. In treating such patients with pre-existing partial heart block, the physician not infrequently is confronted with the difficult decision as to whether digitalis should be prescribed, because of the danger of further interference with the passage of impulses on the one hand, and clear indications for its administration on the other. The proven efficacy of digitalis in patients with normal sinus rhythm^{4,15,18b} has caused this problem to assume increasing importance.

So far as we are aware, no suitable body of evidence bearing on this question is available. Various authorities in the past have expressed conflicting opinions. Thus, Robinson, White, Eggleston and Hatcher²² have stated that "there are certain disorders of the heart which may lead to cardiac failure and which are only exaggerated by the administration of a drug of the digitalis group. In such conditions these drugs are definitely harmful and even dangerous. Cases of partial heart block and a form of cardiac derangement that occurs in diphtheria may be cited as examples.

"In cases of heart block special care and judgment are needed in the use of the digitalis bodies. Depression of conduction is one of the most definite effects that they produce. Therefore, in partial heart block, when further interference with the passage of cardiac

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impulses from auricles to ventricles may be injurious, the digitalis bodies are contraindicated."

Likewise, Cushny^{8a,b} and Edens¹⁰ have expressed the opinion that digitalis affects especially the conducting system of the heart in which auriculoventricular conduction previously has been impaired because of disease. Levy and Mackie¹⁴ have stated, "In partial heart block the danger of further depression of auriculoventricular conduction must be considered; complete block may ensue."

Wenckebach²⁴ declares, "From experiments we may conclude that our therapeutic doses act mainly by their influence on the vagus. In such cases, where conductivity is already impaired, digitalis may do harm, as I predicted as long ago as 1898, and was proved afterwards by many observations.

"The effects of digitalis on heart and circulation being very numerous, we have to reckon with the possibility of a bettered circulation causing a better nutrition of the heart muscle and secondarily improving conductivity and other qualities of the heart. In this way, perhaps, cases in which we saw partial heart block cured by digitalis may be explained."

According to Turnbull,²³ "In cases in which, owing to damage of a-v bundles, the period required for passage of an impulse from auricle to ventricle over the bundle is longer than the normal 0.2 second (a-c interval prolonged), digitalis very frequently further increases this difficulty until some of the impulses fail to pass and a condition of heart block is produced, at first partial, and finally, if the drug be pushed, perhaps complete with blocking of all auricular impulses."

In his excellent treatise on the therapeutic use of digitalis, Robinson²⁰ states, "The depression of conduction is one of the most definite effects which digitalis produces, as has already been brought out. Therefore, in partial heart block, when further interference with the passage of cardiac impulses from auricles to ventricles is decidedly undesirable, digitalis is contraindicated."

Robinson then discusses cases in which conduction time is lengthened and says that cases are seen occasionally in which this is due to faulty nutrition. In such instances this depression may disappear with an improvement in the state of circulation.

It is the opinion of Luten,^{15b} on the other hand, that "its occurrence (lengthening of the *P-R* interval) does not prohibit the further administration of digitalis, but it necessitates great care, and in most instances, it implies that a favorable response is not to be expected."

Similarly, Eggleston has stated,^{11b} "Extensive clinical observations have shown conclusively that while there is an increased tendency for digitalis to enhance a preëxisting depression of conduction or partial block, it is by no means contraindicated in cases of this type. In many such cases it may be administered with satisfactory results

without further prolongation of conduction time or increase in heart block. In others the block, or impaired conduction, seems to be largely secondary to the existence of the heart failure, and when digitalis relieves the failure, the block may disappear or the conduction time may be shortened."

Methods and Materials. Because of these conflicting opinions and the absence of a body of data bearing on this issue, the following study was undertaken. Nineteen patients ranging in age from 15 to 72 years were studied; 13 were males and 6 females. Congestive heart failure was present in almost all. In 14 of the subjects, prolongation of the *P-R* interval was due to coronary sclerosis; in 3 of these there was a varying 2 to 1 and 1 to 1 relationship between auricular and ventricular contractions. The remaining 5 patients had prolonged *P-R* intervals associated with rheumatic heart disease; manifestations of active infection were present in 2.

Digitalis* was administered in doses calculated on the basis of body weight; somewhat less than the full Eggleston dosage was administered.^{11a} In the case of edematous patients the actual weight exclusive of the weight of the edema was estimated and the digitalis administered accordingly, as recommended by Eggleston.^{11a} The actual weight so estimated in almost every case was in close agreement with the weight found after the loss of edema (Table 1). Digitalization was accomplished within 3 to 9 days. A daily utilization of 0.1 gm. was assumed in calculating the amount of digitalis remaining within the body.² Utilization of 0.1 gm. for the first day was excluded since administration was begun usually during the second half of the first day and only negligible amounts could have been utilized. The electrocardiographic tracings following digitalization were taken before the completion of the last day used in the calculation. The errors involved in these calculations tend to give a result too low rather than too high in the calculated amount of digitalis remaining within the body. The dosage per 100 pounds of body weight ranged from 1 to 2.3 gm. and averaged 1.3 gm.

Results. In 6 cases nausea was induced. In the 6 cases in which symptoms of toxicity were precipitated, no significant change in *P-R* interval occurred. In 2 of these patients, changing 2 to 1 and 1 to 1 responses were present before and after digitalization. Of the 19 cases studied, the *P-R* interval did not change in 11; in 3, a lengthening of 0.02 second and in 3 a lengthening of 0.04 second occurred. In 1 patient the *P-R* interval was shortened by 0.04 second and in another the *P-R* interval was shortened by 0.08 second. No alteration in the orderly sequence of auricular and ventricular contractions occurred except that observed in 1 case in which occasional 2 to 1 heart block disappeared and normal 1 to 1 response was established (Table 1).

Discussion. The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given to patients with partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. The dos-

* Powdered leaves, U. S. P. Lederle; 0.1 gm. is equivalent to 1 cat unit. All digitalis used was biologically tested by the manufacturer and again biologically tested by us in cats.

TABLE 1.—DIGITALIS DOSAGE AND P-R INTERVAL.

Sex. Age. Hosp. No.	Diagnosis.	Symptoms and signs.	Associated conditions.	Weight, edema free.	Amount digitalis administered (days), gm.	Digitalis remaining in body (calculated).		P-R interval, sec.		Blood pressure, mm. Hg.		Pulse.		T wave changes.
						Total gm.	Gm./10 lb. body wt.	Before.	After.	Before.	After.	Before.	After.	
M 62 46007	Art. ht. dis., cong. failure	Dyspnea	Coronary occlusion	124	4.2 (14)	2.9*	.23	.24	.24	110/70	120/70	80	45	+
M 51 27319	Hypertension, art. ht. dis., cong. failure	Dyspnea, orthopnea, hepatomegaly, sl. edema and rales	None	120	2.5 (9)	1.7	.14	.22	.22	170/130	140/90	120	80	+
F 72 34239	Hypertension, art. ht. dis., cong. failure	Dyspnea, orthopnea, rales, hepatomegaly, edema, hydrothorax	None	105	1.8 (5)	1.4	.13	.26	.22	160/100	150/100	88	78	+
M 54 19942	Hypertension, art. ht. dis., cong. failure.	Dyspnea, orthopnea, rales, hepatomegaly, edema, hydrothorax	None	130	2.4 (8)	1.7	.13	.24	.24	200/120	180/110	85	65	+
F 50 3172	Hypertension, art. ht. dis., cong. failure	Dyspnea and edema on exertion	Chronic cholecystitis	160	2.1 (4)	1.8	.11	.24	.28	155/75	140/80	70	70	+
M 64 27214	Art. ht. dis., cong. failure	Dyspnea, rales, hydrothorax	Simmonds' cachexia	87	1.3 (4)	1.0	.11	.22	.22	120/80	120/80	85	75	+
M 57 26100	Hypertension, art. ht. dis., cong. failure	Dyspnea, orthopnea, rales, edema	None	110	1.6 (5)	1.2	.11	.24	.28	130/100	120/80	100	80	+
M 70 2201	Hypertension, art. ht. dis., cong. failure	Dyspnea, rales and edema	Diabetes mellitus	170	2.3 (6)	1.8	.11	.24	.24-.28	195/110	200/100	65	65	+

M 67 20821	Art. ht. dis., cong. failure	Dyspnea, orthopnea, rales, hepatomegaly, edema	None	120	1.4 (3)	1.2	.10	.24	.26	130/80	130/80	80	60	+
M 62 45563	Art. ht. dis., cong. failure	Angina pectoris, dyspnea, orthopnea, rales, cardiac asthma	None	142	3.9 (13) ††	?*	?	.28	.28	140/70	140/70	75	65	+
F 60 43762	Art. ht. dis., hypertension, cong. failure	Dyspnea, edema	None	163	1.7 (4) ††	?*	?	.22	.22	145/90	145/90	70	70	?
F 67 7697	Art. ht. dis., cong. failure	Dyspnea on exertion, rales	None	105	1.7 (5)	1.3*	.12	2:1, 1:1	2:1, 1:1	200/80	200/80	50	50	+
F 52 46261	Art. ht. dis.	Angina pectoris, Stokes-Adams syndrome	None	140	2.0 (4)	1.7*	.12	.24-.28 with 3:2 or 2:1 block	.24-.28 with 3:2 or 2:1 block	110/70	110/70	30-50	30-50	+
M 70 35906	Art. ht. dis., cong. failure	Dyspnea, orthopnea, rales, hydrothorax	Acute coronary occlusion	?	1.9 (3)	1.7	?	.23-.26 with 2:1, 1:1 response	NR .28	170/60	170/60	115	80	+
M 35 46104	Rheum. ht. dis., acute rh. fever, cong. failure	Dyspnea, cyanosis, edema	None	141	2.4 (5) 3.0 (12)	2.0* 1.9*	.14 .13	.36 .32-.34	.44 .34-.36	120/60 120/60	120/60 120/60	80 70	65 65	+
M 55 9065	Rheum. ht. dis., mitral insuff., aortic insuff., cong. failure	Dyspnea, orthopnea, rales, hepatomegaly, edema	None	120	2.1 (7)	1.5	.13	.24	.26	200/50	200/50	60	60	+
M 21 9404	Rheum. ht. dis., aortic insuff., mitral sten. and insuff., cong. failure	Dyspnea, orthopnea, rales	None	100	1.8 (6)	1.3	.13	.32	.24	240/0	240/0	90	85	+
M 15 36197	Rheum. ht. dis., mitral sten., aortic insuff., cong. fail.	Dyspnea at rest	Acute rheumatic fever	100	1.4 (4)	1.1	.11	.28	.28	125/65	125/65	100	65	+
F 45 17739	Rheum. ht. dis., mitral sten., aortic insuff.	Cardiac asthma, hemoptyses	None	170	2.6 (9)	1.8	.11	.28	.30	120/60	120/60	75	75	+

* Symptoms of toxicity.

†† These 2 patients were partially digitalized on admission, having previously received an undetermined amount of digitalis.

ages employed were those usually employed in treating patients with congestive failure in the hospital; the adequacy of the amounts used was indicated by the therapeutic response; it was not considered relevant to this study to give amounts which would produce toxic manifestations, although in 6 cases nausea occurred without change in the $P-R$ interval. We are in agreement with the general opinion^{9,14,15b,18a,22,25} that digitalis should not be employed regularly in the largest possible doses on the assumption that the highest level of action that can be induced without intoxication is invariably most effective. Patients often can tolerate much larger doses of digitalis than are necessary to maintain a condition of optimum improvement.^{12,28} The studies of dosage by Eggleston have afforded an invaluable guide in regard to digitalis administration, and, as Luten has stated, "represent quantities which in the average should be regarded rather as doses not to be exceeded than as doses to be administered—as top dosage rather than as optimum dosage." It has been shown that the earliest detectable changes in the T wave occur when approximately 55% of the total estimated therapeutic dose is within the body and that the more pronounced changes occur with approximately 90% of the full therapeutic dosage.² In all instances characteristic pronounced T -wave changes induced by digitalis were evident, indicating that sufficient amounts of digitalis had been administered to attain the therapeutic zone of its action.^{7,15b} In none of the cases studied did the administration of digitalis precipitate auricular fibrillation.

It is of interest that in several patients shortening of the $P-R$ interval was witnessed. This was associated with clinical improvement and presumably is to be attributed to the consequent improved nutrition of cardiac tissue.

It is hardly to be doubted that, if digitalis in greater dosages had been administered, increased lengthening of the $P-R$ interval and even complete heart block could have been induced as is the case with even normal subjects.^{6,13,16,26} In normal individuals changes in the T wave precede changes in auriculoventricular conduction time. The results of the present study indicate that similarly in cardiac patients with partial block the same relationship holds. These considerations are in accord with the experimental findings of Robinson and Wilson²¹ who found, after the intravenous administration of digitalis to cats, that inversion of the T wave appeared after an average of 24% of the fatal dose, definite prolongation of the $P-R$ interval was observed after an average of 52%, ectopic beats after an average of 72% and complete auriculoventricular dissociation was produced by an average of 80% of the lethal dose. Whether excessive doses would produce complete heart block more readily in patients with depressed conduction was not studied, since this question was not considered germane to this investigation and because production of complete dissociation is not without danger.

The production of complete auriculoventricular dissociation, while usually not harmful, may nevertheless result in Adams-Stokes syndrome and therefore is to be avoided.^{19a,b}

The results of this study show that while digitalis and organic heart disease each result in interference with auriculoventricular conduction, these factors do not reinforce each other, and their simultaneous presence does not lead to an additive effect when doses such as used in the present study are utilized.

The findings in Case 46007 are of especial interest in that they demonstrate the difficulty of interpreting the relation of changes in *P-R* interval to the administration of digitalis in patients experiencing an exacerbation of acute rheumatic fever (Table 2). In this instance the administration of digitalis during an exacerbation of rheumatic fever was apparently followed by a marked increase in the length of the *P-R* interval from 0.36 to 0.44 second. However, subsequent digitalization to the point of nausea after the subsidence of the exacerbation of rheumatic fever was associated with no change in *P-R* interval, the latter remaining at approximately 0.34. It is clear, therefore, that the increase in *P-R* interval associated with the first course of digitalis was due not to the drug but rather to the flare-up of rheumatic fever.

TABLE 2.—DIGITALIS DOSAGE AND *P-R* INTERVAL IN CASE 46007.

Date.	Digitalis dose, gm.	<i>P-R</i> interval, sec.	Remarks.
Mar. 730	
2036	Acute rheumatic fever.
2336	
248		
256		
265		
274	.44	
281	.44	Nausea.
2942	
3038	
3144	Subsidence of rh. fever.
April 132	
334	
53	.34	
6 (A.M.)3	.36	
6 (P.M.)34	Nausea.
736	

As Luten^{15b} has pointed out, the failure of an auricular impulse to elicit a ventricular response is explainable on either of two suppositions: (a) either the impulse fails to reach the ventricle, or (b) reaching it, finds the ventricle unresponsive. The lengthened *P-R* interval associated with active rheumatic carditis has been shown by Bruenn³ to be largely vagal in origin; that associated with arteriosclerotic heart disease may be similar or due to structural changes in the auriculoventricular conduction system.¹

In both instances the effect is on the conduction system either

directly because of a pathologic lesion or indirectly through the vagus nerves. However, there is much evidence, clinical and experimental, to show that heart block due to digitalis in therapeutic dosage is referable, in part at least, to the action of the drug upon the musculature of the ventricle, rendering it less excitable to auricular stimuli.^{16b} The results reported in this study would seem to be in accord with this concept.

Finally, attention should be drawn to the fact that, although digitalis in doses of 0.1 to 0.23 gm. per 10 pounds of body weight did not greatly increase preëxisting heart block in any case of this series, it is impossible to preclude the possibility that occasional or rare instances may be encountered in which this may occur, particularly if dosages approaching toxic amounts are employed. Certain observers have stated that complete heart block has been observed to occur when only small or moderate doses were given to patients with partial heart block.²⁷ Caution and careful observation, therefore, should be exercised, particularly if larger doses than those employed by us are utilized.

Summary and Conclusions. In treating patients with preëxisting partial heart block, the physician is not infrequently confronted with the difficult decision as to whether digitalis should be prescribed, because of the danger of further interference with the passage of impulses on the one hand, and clear indications for its administration on the other. So far as we are aware, no suitable body of evidence bearing on this question is available.

Nineteen patients ranging in age from 15 to 72 years were studied. Congestive heart failure was present in almost all subjects. In 3, a varying 2 to 1 and 1 to 1 relationship between auricular and ventricular contractions existed. In most of the patients prolongation of the *P-R* interval was due to coronary sclerosis; in the others, rheumatic heart disease was present.

A standardized preparation of digitalis was administered in doses calculated on the basis of body weight; in accord with general practice, somewhat less than the full Eggleston dosage was administered.

The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given to patients with partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. The dosages employed were those usually employed in treating patients with congestive failure in the hospital; the adequacy of the amounts used was indicated by the therapeutic response; it was not considered germane to this study to give amounts which would produce toxic manifestations, although in 6 cases nausea occurred without change in the *P-R* interval.

The results of this study show that while digitalis and organic heart disease each result in interference with auriculoventricular conduction, these factors do not reinforce each other and their simul-

taneous presence does not lead to an additive effect when doses in therapeutic amounts such as were used in the present study are utilized. The presence of partial heart block does not constitute a contraindication to the use of digitalis.

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EXPERIMENTAL ARTHRITIS IN RABBITS PRODUCED WITH STREPTOCOCCI AND OTHER ORGANISMS.*†

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ALTHOUGH it has been known for over 50 years that arthritis can be readily produced in rabbits with various strains of streptococci, there have been few experimental studies on the pathogenesis and course of infectious arthritis.

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There are many reports on attempts to produce acute or chronic arthritis in rabbits with various strains of streptococci. One group of experiments has been reported by those who have tried to reproduce the pathologic picture of acute rheumatic fever in rabbits with organisms obtained from the blood and joints of patients with that disease.^{2,10,14,16,18-21}

Another group, interested in chronic arthritis, has produced lesions in the joints of rabbits with various streptococci obtained from cultures of the blood, throat or teeth of patients with chronic infectious arthritis. They concluded that because these organisms produced arthritis so readily in rabbits, they were probably of etiologic significance in the disease.^{3,8,9,12}

Cole,⁴ Davis⁶ and McMeans,¹⁵ however, showed that the source of these so-called arthrotropic streptococci was of little importance so far as the production of arthritis in rabbits is concerned. These authors demonstrated that streptococci obtained from patients with peritonitis, puerperal septicemia, empyema, appendicitis, scarlet fever, endocarditis, and nephritis produced arthritis in rabbits as readily as did streptococci obtained from patients with arthritis.

Jackson¹¹ made a careful histologic study of the joints of rabbits in which arthritis had been produced by intravenous injections of hemolytic streptococci obtained from the tonsils of patients during the epidemic of sore throat in Chicago in 1911 and 1912. The doses of bacteria injected were so large that in many instances the joints were completely destroyed. Hadjopoulos and Burbank⁹ made a histologic study of the joints in experimental arthritis in rabbits. They have attributed the chronic character of the lesion produced to the fact that the streptococci used in their experiments were avirulent and obtained from cases of chronic arthritis. No control experiments were reported. Jarløv and Brinch¹² have also recently reported an experimental study of streptococcus arthritis in rabbits. They made a detailed study of the nature of the joint lesions and have attributed much importance to the fact that the organisms used came from patients with arthritis. However, they have not used a sufficient number of organisms from other sources as controls.

Our chief object in undertaking the present investigation was to study the pathogenesis of streptococcus arthritis in rabbits. However, since little attention has been given to any organism other than the streptococcus so far as the production of experimental arthritis is concerned, it seemed advisable for us to include several other types of bacteria in such a study.

Method. Healthy albino rabbits that weighed from 1800 to 2400 gm. have been used throughout the experiments. The majority of the animals were males.

Two cultures of Group A hemolytic streptococci (Strains AB 13 and NY 5) and one of *Strep. viridans* were used. Strain AB 13 was obtained from the

blood of a patient with rheumatoid arthritis,¹⁷ and Strain NY 5 was isolated from a case of scarlet fever by Dochez. The strain of *Strep. viridans* was freshly isolated from the blood of a patient with subacute bacterial endocarditis.

To determine the arthritis-producing capacity of several other bacteria, we have used the following for intravenous injection: *Staph. aureus*, *Pneum. Types 1 and XIV*, *B. paratyphosus A*, *B. typhosus*, *B. coli communior*, *B. dysenteriae* (Flexner), *Proteus X 19*, *Br. abortus* and *Br. melitensis*.

Most of the rabbits were given single intravenous injections of an 18-hour broth culture; some received more than one injection. The dose (Table 1) was varied according to the virulence of the organism.

They were bled from the ear vein before injection, after that at 2, 4 and 8 weeks, and then at monthly intervals to determine the sedimentation rate and the agglutinin titre of the sera. The fall of the red blood cells was recorded in millimeters per hour. In order to determine the sensitivity of the animals to streptococci, skin tests were done on a large number of animals with an homologous 48-hour broth filtrate. Frequent Roentgen-ray examinations were made of the involved joints.

A considerable number of the affected joints were aspirated and the synovial fluid examined and cultured. Blood cultures were taken frequently during life and routinely at autopsy. Complete autopsies were performed in every instance, and the joints opened and examined. The synovial fluid, as well as the synovial tissue, of the affected joints was usually cultured. Smears of the exudate were made in order to study the cytology and to determine whether organisms were present.

TABLE 1.—INCIDENCE OF ARTHRITIS PRODUCED IN RABBITS WITH A SINGLE INTRAVENOUS INJECTION OF DIFFERENT STRAINS OF STREPTOCOCCI.

Organism.	Dose in cc.	No. of rabbits.	Rabbits with arthritis.	
			Number.	Per cent.
<i>Strep. hemolyticus</i>	4.0	5	5	100.0
Strain AB 13	2.0	25	17	68.0
	1.0	21	7	33.3
	0.1	25	6	24.0
<i>Strep. hemolyticus</i>	1.0	6	5	83.3
Strain NY 5	0.5	20	13	65.0
<i>Strep. viridans</i>	2.0	22	11	50.0
	1.0	2	1	50.0

Incidence of Arthritis in Relation to the Dose and the Number of Intravenous Injections. A group of 76 rabbits received single intravenous injections of broth culture of hemolytic streptococcus (Strain AB 13). The dose varied from 0.1 to 4 cc. (Table 1). Of 13 additional rabbits that received less than 0.1 cc., none developed arthritis. It is obvious that the larger doses produced arthritis more readily than did the smaller. An occasional animal died from 4 cc. of culture, whereas smaller amounts were never fatal. From this series of animals it was evident that a single injection of 2 cc. of broth culture was the most suitable dose with which to produce arthritis in a fairly high percentage of animals. It is of interest that one-half of this dose (1 cc.) produced arthritis in only 33% of the injected rabbits, whereas the larger dose (2 cc.) produced arthritis in 68%. Another group of 39 rabbits received 3 injections of 0.1, 1 and 2 cc.

respectively of the same strain of streptococcus at 10-day intervals, and of these 36 (92.3%) developed arthritis.

Eighteen of 26 rabbits developed arthritis following an intravenous injection of *Strep. hemolyticus* (Strain NY 5) in amounts of 0.5 or 1 cc. It was necessary to use somewhat smaller doses of this organism because, when more than 1 cc. of culture was injected, the animal usually died. Although an occasional animal died after 0.5 cc. of culture, this was a satisfactory dose for the production of arthritis.

Twelve of 24 rabbits that received 1 or 2 cc. of *Strep. viridans* culture intravenously, and 2 of 4 rabbits that received more than one injection, developed arthritis.

When one compares the incidence (Table 1) of arthritis produced by the 3 strains of streptococci with doses of about the same size, it is evident that Strain NY 5 produced arthritis somewhat more frequently in our series than did Strain AB 13. Seventeen (68%) of 25 rabbits injected with 2 cc. of Strain AB 13 developed arthritis, whereas 5 (83.3%) of 6 injected with 1 cc. and 13 (65%) of 20 injected with 0.5 cc. of NY 5 developed arthritis. *Strep. viridans* produced arthritis in 11 (50%) of 22 rabbits that received 2 cc. of culture intravenously.

TABLE 2.—PRODUCTION OF ARTHRITIS WITH A SINGLE INTRAVENOUS INJECTION OF VARIOUS ORGANISMS.

Organism.	Dose in cc.	No. of rabbits.	Rabbits with arthritis.	
			Number.	Per cent.
<i>Staph. aureus</i>	0.05-2.0	17	13	76.5
<i>Pneumococcus</i>	1.0-2.0	11	4	36.4
<i>B. paratyphosus</i> A . . .	1.0-2.0	6	1	16.7
<i>B. typhosus</i>	1.0-2.0	6	0	0
<i>B. coli communior</i> . . .	0.5-2.0	7	0	0
<i>B. dysenteriae</i> Flexner . .	0.01-0.1	6	0	0
<i>Proteus</i> X 19	0.5-2.0	6	0	0
<i>Br. abortus</i>	2.0	6	0	0
<i>Br. melitensis</i>	2.0	6	0	0

In order to determine the incidence of arthritis produced with organisms other than streptococci, 71 animals (Table 2) were injected. Of 17 that received *Staph. aureus*, 13 (76.5%) developed arthritis. Nineteen additional rabbits died within 3 days after the intravenous injection. Four of 11 rabbits injected with *Pneumococcus* and 1 of 6 with *B. paratyphosus* A developed arthritis, whereas none of the 37 rabbits that received injections of *B. typhosus*, *B. coli communior*, *B. dysenteriae* (Flexner), *Proteus* X 19, *Br. abortus* or *Br. melitensis*, did so.

Incidence of Arthritis in Relation to Sex. The animals were selected for these experiments without regard to sex, although the majority were males. When we analyzed the development of arthritis in relation to sex, the results indicated that arthritis occurred more frequently in females than in males. Only those that received single comparable doses of the same organism were included.

Thirty (40.5%) of 74 male rabbits developed arthritis as contrasted with 21 (75%) of 28 female rabbits. Many uncontrolled factors other than sex may have been responsible for this difference.

Observations on the Course of Arthritis. The animals were observed daily for 10 days and thereafter at frequent intervals to determine whether arthritis developed. When a joint became involved, the rabbit favored the affected extremity by holding it off the floor and by hopping or limping. Arthritis usually developed from the 3rd to the 7th day, although it was occasionally observed within 48 hours or as late as 12 days after injection. One could readily localize the affected joint by palpation. There was usually swelling, increase in surface temperature and, occasionally, fluctuation. In many instances the swelling rapidly subsided, and the animal began to use the joint again within 2 to 3 weeks. Although arthritis was frequently observed in several joints in the same animal, it did not develop in additional joints after the first 12 days. If the swelling did not subside within a short time, the joints frequently remained involved for several months and in this case there was often proliferation of bone, increase of fibrous connective tissue and partial ankylosis. The progress of the alterations in the bony structures of the joint was followed by means of Roentgen-ray photographs. The protocol of 1 rabbit in which these chronic changes occurred may be of interest.

Rabbit 119: Two cubic centimeters of an 18-hour broth culture of hemolytic streptococci (Strain AB 13) were injected intravenously on December 31, 1936. Eleven days later the animal held the right leg flexed; there was swelling of the right knee joint and pain on movement. The joint was aspirated, and a large number of neutrophils and a few cocci were seen in a smear of the synovial fluid. Hemolytic streptococci were grown in culture. The knee joint was aspirated 12 days later; there were fewer neutrophils and a considerable number of monocytes in the synovial fluid, a culture of which was sterile. After 6 months (Fig. 1) the joint was still swollen, tender and flexed, and there was crepitus on movement. Except for a slight decrease in swelling, there was no change for 23 months. The serum agglutinins against Strain AB 13 increased during the first 2 months up to 1:1280, but were not present after 4 months. The sedimentation rate increased to 45 millimeters per hour during the first 2 months and returned to normal after 4 months. At autopsy the right knee joint revealed no excess of synovial fluid; the synovial membrane, however, was thicker than normal. The cartilage had lost its normal lustre, and there was considerable degeneration of both bone and cartilage over the lower end of the femur. The cruciate ligaments were thick and shortened, and the joint could not be fully extended. Cultures of synovial tissue were sterile. Microscopically, the joint capsule and synovia showed an increase of fibrous connective tissue but no cellular infiltration.

One group of 22 rabbits that developed arthritis was permitted to live until gross or Roentgen-ray evidence of arthritis had disappeared, or were killed at intervals for bacteriologic and histologic study. The average duration of arthritis in these rabbits was about

15 weeks. One animal that received a single intravenous injection of hemolytic streptococci 2 years previously is still living and has a chronic arthritis of the right elbow associated with partial ankylosis.

The distribution of the joints in which arthritis developed in 198 rabbits was as follows: 130 shoulders, 89 knees, 42 elbows, 39 wrists, 12 hips, 8 interphalangeals, and 6 ankles. In a few animals more than one of the contralateral joints were involved.

Bacteriologic Studies of Blood and Joints. Blood cultures were taken on many animals for several days after injection. The organisms rapidly disappeared from the blood and were seldom recovered in cultures after about the 5th or 6th day. Routine cultures of the heart blood and in several instances, of the spleen, were made at autopsy. These were always sterile in animals that lived for 2 or more weeks following injection.

TABLE 3.—RESULTS OF CULTURES OF SYNOVIAL FLUID AND TISSUE.

Weeks after injection.	Synovial fluid (aspirated)		Synovial fluid (postmortem)		Synovial tissue (postmortem)	
	Growth.	No growth.	Growth.	No growth.	Growth.	No growth.
1	3	3	7	2		
2	4	11	6	7	4	2
3	1	5	6	11	7	11
4-6			5	8	6	8
6-8	0	1	1	3	0	2
8-10	1	0	0	13	2	14
10-12			0	2	0	2
12-60			0	7	0	12
Totals	9	20	25	53	19	51

Affected joints were aspirated (Table 3) at intervals to obtain synovial fluid for culture and cytologic study. During the first 3 weeks of arthritis the exudate within the joint cavity was opaque and viscid, but although it contained many neutrophils was seldom purulent. It was purulent, however, in animals that had received large doses or repeated intravenous injections of hemolytic streptococci. Streptococci were readily grown from aspirated synovial fluid during the first week, and after that with increasing difficulty. Aspirations were not done repeatedly, nor on a greater number of animals, because of the trauma caused by this procedure. Cultures of the synovial fluid and tissue at autopsy were usually sterile after the 6th week (Table 3), although organisms were recovered in a few instances 8 weeks after injection. The synovial fluid gradually became clear but was present in excess for several months.

To determine how long organisms would remain viable in the joint 4 cc. of a broth culture of hemolytic streptococci (Strain AB 13) concentrated to a volume of 0.1 cc., were injected into the right knee joint of 12 rabbits (Table 4). Seven rabbits were given single injections, and 5 received multiple injections. The animals were killed at intervals of from 9 to 81 days. Of those that



FIG. 1.—Swelling of the right knee joint of Rabbit 119, 6 months following an intravenous injection of 2 cc. of broth culture of hemolytic streptococcus (Strain AB 13).

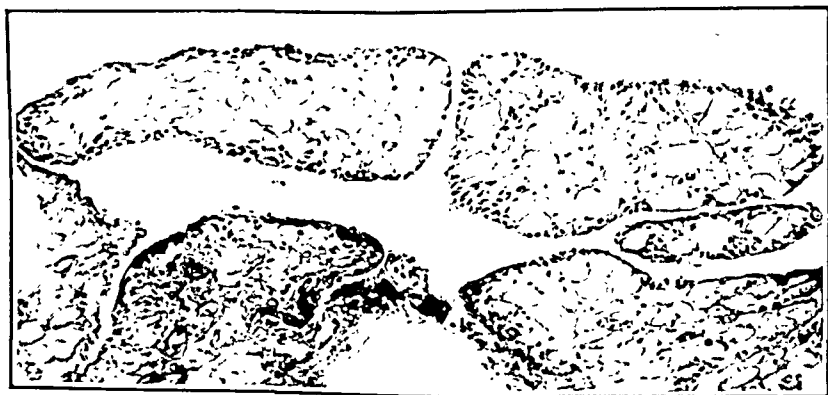


FIG. 2.—Synovial villi from a normal knee joint. ($\times 170$.)

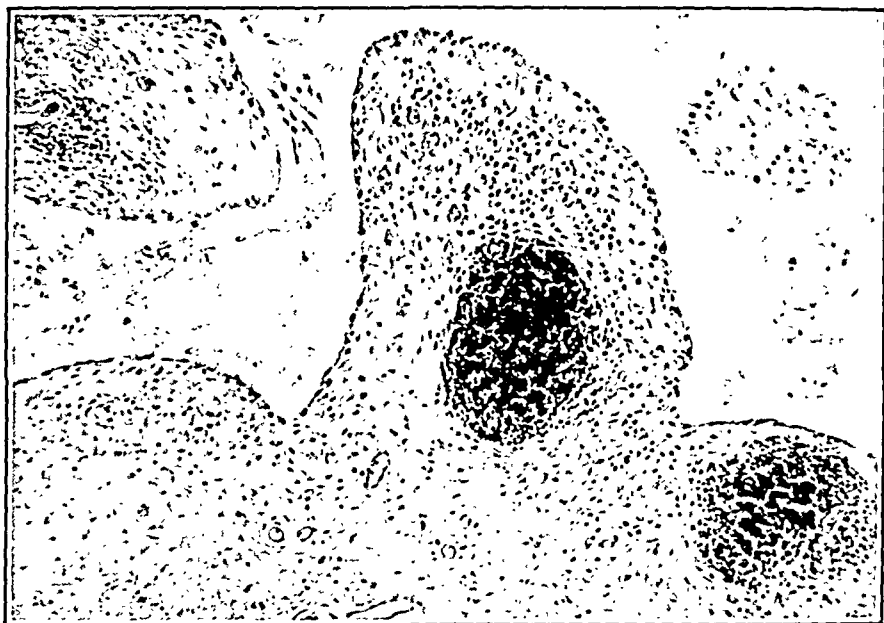


FIG. 7.—From the same section shown in Figure 6. Note the dense collection of lymphocytes in the subsynovial tissue. ($\times 170$.)

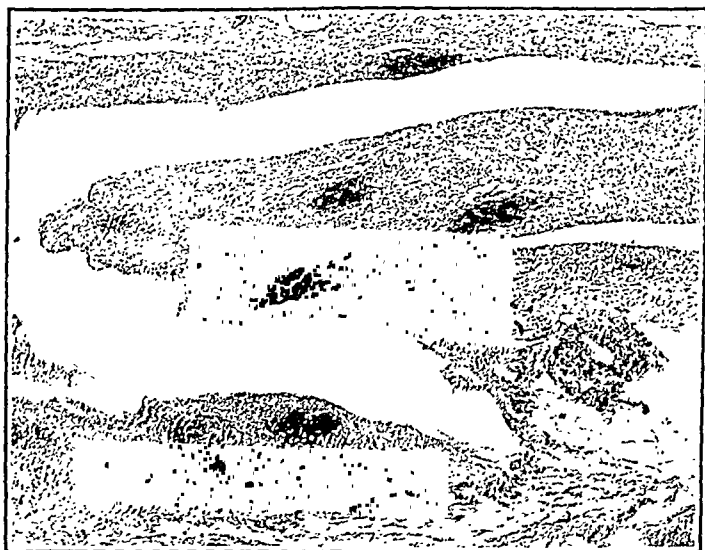


FIG. 8.—Section of synovial tissue from the left knee joint of a rabbit 43 days after an intravenous injection of 2 cc. of a broth culture of pneumococcus Type XIV. Note the focal accumulation of lymphocytes. ($\times 68$.)

received single injections, streptococci were not recovered from the synovial fluid or tissue after 21 days, and in only one of the 5 rabbits that had received multiple injections were organisms recovered from the joint as late as 30 days after the last injection.

TABLE 4.—RESULTS OF CULTURE OF JOINTS AFTER INTRA-ARTICULAR INJECTIONS OF HEMOLYTIC STREPTOCOCCUS (STRAIN AB 13).

Rabbit number.	Dose in cc.	Days after injection.	Material cultured.	
			Synovial fluid.	Synovial tissue.
1	4.0	9	Growth	Growth
2	4.0	21	Growth	Growth
3	4.0	35	No growth	No growth
4	4.0	40	No growth	No growth
5	4.0	51	No growth	No growth
6	4.0	63	No growth	No growth
7	4.0	81	No growth	No growth
8	4.0*	30	Growth	Growth
9	4.0*	30	No growth	No growth
10	4.0*	30	No growth	No growth
11	4.0*	30	No growth	No growth
12	4.0*	30	No growth	No growth

* 3 injections.

Serologic Tests. The sedimentation rate and agglutination titre were determined on all animals injected with hemolytic streptococci at 2, 4 and 8 weeks and thereafter at monthly intervals as long as the animals survived. Skin tests were done on 48 rabbits in order to determine sensitivity to streptococcus filtrate. The results, recorded in Table 5, are concerned only with those animals on which several observations were made.

TABLE 5.—THE SEDIMENTATION RATE, AGGLUTINATION TITRE AND SKIN TEST IN RABBITS THAT RECEIVED INTRAVENOUS INJECTIONS OF HEMOLYTIC STREPTOCOCCI.

	Sedimentation rate.			Agglutination titre.			Skin test.		
	No. of rabbits.	No. increased.	%	No. of rabbits.	No. positive.	% positive.	No. of rabbits.	No. positive.	% positive.
With arthritis	35	34	97.1	55	49	89.1	43	18	41.8
With no arthritis	12	10	83.3	13	5	38.4	5	2	40.0

The sedimentation rate usually increased during the first month and returned to normal within 2 months. It was increased in 34 (97.1%) of 35 rabbits that developed arthritis and in 10 (83.3%) of 12 injected rabbits in which no arthritis was demonstrated.

The agglutination titre was determined on the sera of many animals before injection, and in no instance did they agglutinate cultures of hemolytic streptococci. Agglutinins were present within 2 weeks after inoculation, reached a maximum after 1 month and slowly disappeared unless the animal were reinfected. The titre usually varied directly with the dosage. Agglutinins were demonstrated in 49 (89.1%) of 55 injected rabbits that developed arthritis and in 5 (38.4%) of 13 in which there was no arthritis.

Of the 48 animals on which skin tests were made with a homologous streptococcus filtrate, sensitivity was demonstrated in 18 (41.8%) of 43 with arthritis and in 2 (40.0%) of 5 that did not develop arthritis.

TABLE 6.—INCIDENCE OF ARTHRITIS PRODUCED BY THE INJECTION OF HEMOLYTIC STREPTOCOCCI (STRAIN AB 13) INTO VARIOUS SITES.

Site of injection.	No. of rabbits.	Rabbits with arthritis.	
		Number.	%
Gum	16	7	43.8
Maxillary sinus	17	4	23.5
Knee joint	16	2*	12.5
Kidney pelvis	16	1	
Eye	13	1	
Pleural cavity	11	1	
Prostate	7	1	
Uterus	7	1	
Testis	5	0	0
Fallopian tubes	5	0	0
Skin	10	0	0
Peritoneal cavity	10	0	0
Gall bladder	6	0	0
Nose	4	0	0
Oral cavity	4	0	0
Total	147	18	12.2

* Arthritis observed in non-injected joints.

The Production of Arthritis by the Injection of Hemolytic Streptococci (Strain AB 13) into Various Sites. The following experiment was undertaken to study the production of arthritis in rabbits injected by other than the intravenous route, and the relationship of the invasion of the blood stream to the subsequent development of arthritis. An attempt was made to establish foci at various sites in rabbits by means of single or multiple injections of bacteria (Table 6). The usual dose was 4 cc. of an 18-hour broth culture concentrated to a volume of about 0.1 cc. The following methods were used:

1. Suspensions of hemolytic streptococci were injected into the following: the gum, maxillary sinus, prostate, testis, anterior chamber of the eye, pleural and peritoneal cavities, joint and skin.
2. Segments of the uterus or Fallopian tubes were isolated by ligature and injected.
3. The renal pelvis was injected after ligation of the ureter.
4. The gall bladder was injected after ligation of the cystic duct.
5. The animals in one group were fed large amounts of hemolytic streptococcus cultures over a considerable period of time.
6. Pledgets of cotton were soaked with streptococci and packed firmly into the nares where they remained for several weeks.

The injected organisms usually produced a localized abscess at the site of injection. However, it was difficult to establish an infected focus from which streptococci could be recovered longer than from 2 to 3 weeks after injection. By means of the sedimentation rate

and agglutinin titre of the blood, we were able to obtain some evidence as to how long the focus of infection persisted. The focus was cultured at autopsy and in most instances was sterile.

We were, however, successful in establishing a focus in the eye with small doses of streptococci and were able to recover organisms from it 30 days after a single intraocular injection. Arthritis developed in only 1 of 13 of these rabbits, and it appeared within 6 days after injection.

Arthritis was noted in 18 (12.2%) of 147 rabbits (Table 6) within a few days after infection. It was observed in 7 (43.8%) of 16 rabbits injected into the gums and in 4 (23.5%) of 17 injected into the maxillary sinuses. Arthritis also developed in a few of the animals that had received injections of streptococci into the knee joint, kidney pelvis, eye, pleural cavity, prostate or uterus.

To determine to what extent organisms invaded the circulation, blood cultures were made on most of the animals at intervals of 1, 6, 24 and 48 hours after injection. In the group of rabbits injected into the gums (Table 7) arthritis developed in all 6 of the animals with positive blood cultures and in only 1 of 10 with sterile cultures. Of 102 rabbits, 12 (26.7%) of 45 with positive blood cultures developed arthritis in contrast to only 4 (7.0%) of 57 with negative blood cultures. When animals were injected repeatedly into the same site, the blood was cultured following each injection. Streptococci were frequently recovered after the first injection but were seldom found after subsequent injections.

TABLE 7.—EXPERIMENTAL ARTHRITIS IN RELATION TO INVASION OF THE BLOOD STREAM AFTER INJECTION OF HEMOLYTIC STREPTOCOCCI INTO THE GUMS.

Rabbit number.	Colonies per cc. of blood.				Arthritis.
	1 hr.	6 hrs.	24 hrs.	48 hrs.	
1 . . .	1	1	110	5	+
2 . . .	4	14	22	1	+
3 . . .	8	4	15	3	+
4 . . .	39	22	115	320	+
5 . . .	12	3	3	2	+
6 . . .	40	10	22	2	+

Pathologic Anatomy. Although there are adequate anatomic descriptions of the synovial villi of joints, they have been almost entirely overlooked in previous reports of experimental arthritis. It soon became evident that the villi must be considered in any study on pathogenesis, and the knee was found to be most satisfactory for such a study.

When the joint of a rabbit is opened, the synovial lining is normally smooth and glistening. If it is submerged in saline and examined with a dissecting microscope, one sees minute floating villi which are somewhat larger at the free ends than at the point of attachment and are either single or branched. A fine network of blood vessels is readily seen through the membrane. In addition

to villi there are also small folds of synovia and tissue. Both the villi and synovial folds are most numerous at the junction of synovia and cartilage and also at the site of ligamentous attachments. Villi are numerous over the infra-patellar pad of fat and at the site of the hinge joint in the patella. When one prepares sections of normal rabbit joints for histologic examination, folds of synovia are frequently seen, but intact villi are rare. Their site is usually represented by a loss of continuity in the synovial membrane. If, however, at autopsy, fixative is injected into the joint with a fine needle, using care not to distend the joint capsule, the villi are fixed in their normal relationship so that they are readily seen in sections from joints prepared in this manner (Fig. 2).

When streptococci lodge in the joints of rabbits after intravenous injection, they cause an extensive accumulation of neutrophils in the synovial fluid which increases in amount and becomes viscid and opaque. Streptococci are present in smears and are readily cultured. The inflammatory exudate usually appears first in synovial villi (Fig. 3) which become large and edematous with an infiltration of neutrophils throughout the synovia and subsynovial tissue. Within 48 hours monocytes and lymphocytes are present in fairly large numbers. The subsequent findings depend upon whether the arthritis heals or persists as a chronic infection.

When arthritis persists for 3 or more weeks, the acute inflammation in the synovial membrane subsides, and the synovial fluid contains fewer cells. In some instances after 12 weeks the villi were prominent and visible with the naked eye (Fig. 4). A photomicrograph of these villi is shown in Figure 5.

After from 4 to 6 weeks, mononuclear leukocytes, lymphocytes and plasma cells predominate, although neutrophils are still present. Considerable numbers of fibroblasts are also seen throughout the subsynovial tissue. Lymphocytes accumulate beneath the synovial membrane as well as about small capillaries (Fig. 6) in the granulation tissue. As they increase in number, they form dense focal collections (Fig. 7) which in some instances resemble lymph follicles (Fig. 5), although no definite germinal centers are observed. Similar collections of lymphocytes, frequently associated with fibrosis of marrow, are seen in the epiphyses adjacent to the affected joints. The blood vessel walls are thicker than normal, and there is proliferation of the endothelium with narrowing of the lumen. In some sections there is a pannus of fibrous connective tissue over the cartilage often associated with degeneration of both hyaline cartilage and bone. Deposits of amyloid were present in the liver, kidney and spleen of a few rabbits with chronic arthritis that lived for several months.

Staphylococci produced extensive suppuration in the joints, but when the acute inflammation had subsided, there were no conspicu-

ous differences from the streptococcus arthritis previously described. That produced with pneumococci (Fig. 8) was also very similar to streptococcus arthritis. However, since we had comparatively few rabbits infected with staphylococci or pneumococci, we were unable to make any detailed study of the pathologic lesions produced in the joints with these organisms.

Discussion. Although various strains of streptococci readily produce arthritis in rabbits, it is evident that other organisms, namely staphylococci and pneumococci, can do so almost as well, but probably somewhat less consistently.

Of the bacteria employed in these investigations, a hemolytic streptococcus (Strain AB 13) obtained from a patient with rheumatoid arthritis,¹⁷ proved to be a satisfactory organism with which to produce arthritis in rabbits although it had been carried on laboratory media for about nine years. The two other strains of streptococci that produced arthritis in a high percentage of instances were not obtained from patients with arthritis. These findings are in accord with those of Cole,⁴ Davis⁶ and McMeans¹⁵ who state that the source of the streptococcus has little to do with the property of elective localization.

Our experiments on the pathogenesis of infections in joints indicate that the anatomic structure of the synovial villi may be as important as the capacity of various microorganisms to localize in the synovia.

Since the hemolytic streptococcus, if not the actual etiologic agent, may be connected in some manner with rheumatoid arthritis, it is necessary to consider whether the experimental arthritis is in any way comparable to the human disease. Experimental infectious arthritis occurred more frequently in female than in male rabbits. The sedimentation rate was increased but rapidly returned to normal. Agglutinins for hemolytic streptococci were demonstrated in a fairly high percentage of animals but did not persist for any length of time. The alterations in sedimentation rate and agglutinin titre were observed, however, in rabbits that did not develop arthritis. The experimental disease was never migratory; furthermore, the involved joints were not those usually affected in rheumatoid arthritis. The latter point is not entirely comparable, because of differences in function of similar joints in rabbit and man.

When the acute inflammation in the infected joint subsides and the arthritis has become chronic, the pathologic picture is very similar to that described as typical of rheumatoid arthritis in man.^{7,1} The question then arises whether the histopathology of the joints in rheumatoid arthritis is sufficiently characteristic to be considered specific. The more material one examines from patients with various types of joint disease, the more one is impressed by the fact that the

pathologic picture of rheumatoid arthritis may not be specific.⁵ A similar lesion can be produced in the synovial tissue of animals by a variety of agents. The character of the lesion in many instances is probably modified as much by the manner of the response of the synovia to an irritant as by any particular property of that irritant. This point has been well illustrated by Jordan.¹³ He shows a photomicrograph of an inflammatory process in the synovial tissue of rabbits which was produced by turpentine and which is indistinguishable from the experimental streptococcal arthritis we have described.

Summary and Conclusions. 1. When small doses of various strains of streptococci were injected intravenously into rabbits, an acute arthritis was produced in several joints and in many instances became chronic. Experimental arthritis was successfully produced with both *Strep. hemolyticus* and *Strep. viridans*. The type of disease from which the streptococcus was isolated bore no relationship to its capacity to produce arthritis. Repeated injections considerably increased the incidence of arthritis.

2. Of several other species of bacteria injected, only *Staph. aureus*, *Pneumococcus* and *B. Paratyphosus A* produced arthritis. The pathologic picture was very similar to that produced with streptococci.

3. Arthritis was observed more frequently in female than in male rabbits.

4. Arthritis usually appeared within a few days after intravenous injection during the stage of bacteremia and seldom developed after the streptococci had disappeared from the circulation.

5. Streptococci were repeatedly grown from synovial fluid during the first 2 or 3 weeks after injection and occasionally from the synovial fluid or tissue as late as 10 weeks.

6. The sedimentation rate was increased in 97.1% and the agglutinin titre elevated in 89.1% of the animals that developed arthritis. The skin test with streptococcus filtrate was positive in only 41.8%. Similar results were obtained in rabbits that did not develop arthritis.

7. Arthritis was produced in 18 (12.2%) of 147 rabbits injected by other than the intravenous route. It occurred most frequently following injection into the gums or sinuses. However, the development of arthritis in these animals was related to the degree of bacterial invasion of the blood stream during the first 48 hours after injection rather than to a later dissemination of bacteria from an infected focus.

8. The pathologic lesion of the synovia in chronic streptococcus arthritis in rabbits is very similar to that commonly associated with rheumatoid arthritis in man. However, in our opinion the specificity of the synovial lesions in rheumatoid arthritis has not yet been established.

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CLINICAL EXPERIENCE WITH GLOBIN INSULIN.

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IN the non-diabetic, insulin activity fluctuates with the amount of glucose that enters the blood stream; that is, it is greater during the postprandial periods. It does not seem probable that a depot preparation can ever be sufficiently controlled to fulfill this requirement. However, a product that exerts its maximum activity during the day, when food is being assimilated, is preferable to one that releases the hormone continuously at a more or less even rate during the entire 24 hours. For, when the latter is injected daily, it may produce a hypoglycemia which becomes most disturbing during the early morning hours, a time when insulin shock is easily overlooked. Protamine zinc insulin, whether administered in the evening or in the morning, is apt to have this effect. In severe cases of diabetes it is usually necessary to supplement protamine zinc insulin with standard insulin.

Other disadvantages¹ observed in the use of protamine zinc insulin are local reactions at the site of injection, possibly allergic in nature, and the inaccuracy and inconvenience of injecting a suspension.

It is apparent that further search for an insulin compound with more desirable properties is warranted.

Of the various preparations tested on rabbits and dogs,² it was found that a combination of globin insulin and zinc seemed to be

most promising. Its action lasts more than twice as long as that of standard insulin, yet it develops its full activity not much later (see curves). This is in marked contrast to protamine zinc insulin, which in rabbits reaches its full activity only after 10 hours, yet the effect is prolonged over 24 hours when only 0.5 unit per kg. (an amount comparable to 25 to 35 units for man) is administered.

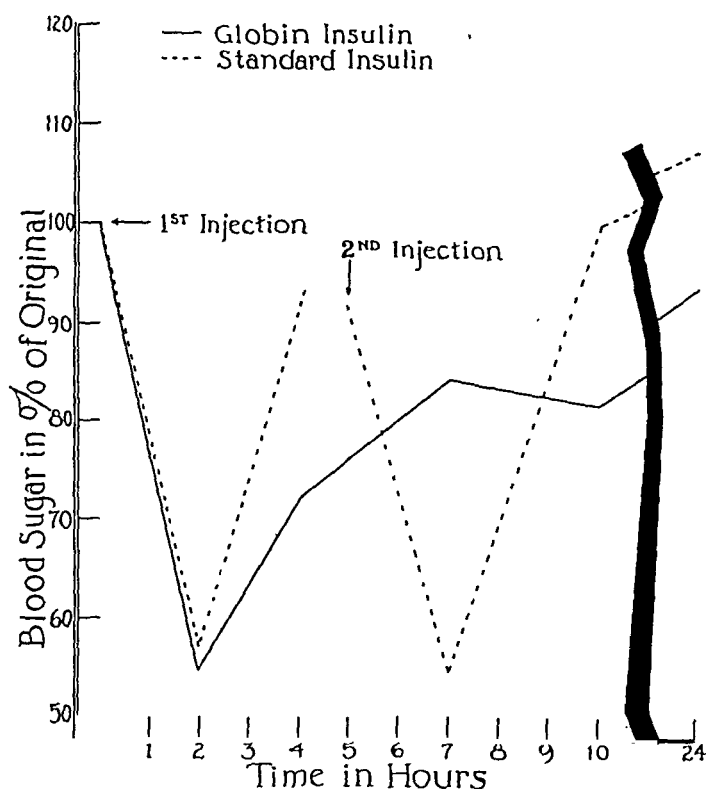


FIG. 1.

FIG. 1.—COMPARISON OF THE EFFECT OF GLOBIN AND REGULAR INSULIN. Globin insulin (0.8 unit per kg.) was injected into 15 fasting rabbits; regular insulin (0.4 unit) was injected into 15 fasting rabbits and repeated in 5 hours. After 10 hours the effect of globin insulin is still apparent, in fact, the normal fasting blood sugar is not reached in 24 hours; whereas after 2 doses of regular insulin the blood sugar values are above normal at this time. To counteract the effect of individual differences in insulin sensitivity, the experiments were reversed or "crossed" after an interval of 1 week.

Our preparation consisted of a mixture of 80 units of insulin per cc. with native globin in the proportion of 1000 units of insulin to 38 mg. of globin and 3 mg. of zinc (as ZnCl_2). When used as a suspension it was buffered to a pH of 6.1 with Na_2HPO_4 . More than 99% of the insulin in this preparation was found in the precipitate and less than 0.5 unit per cc. was found in the supernatant liquid. We also used a clear globin solution at a pH of 4. Neither animal experi-

ments nor clinical experience showed any difference between the two preparations which would be significant from a practical standpoint.

Animal experiments having excluded toxicity of the globin even in relatively large and repeated doses, we proceeded to study the effect of the globin insulin preparation on normal human beings. In 5 subjects, 10 units injected 15 hours after the last meal, produced a minimum blood sugar in 4 to 6 hours, ranging from 60 to 80 mg.

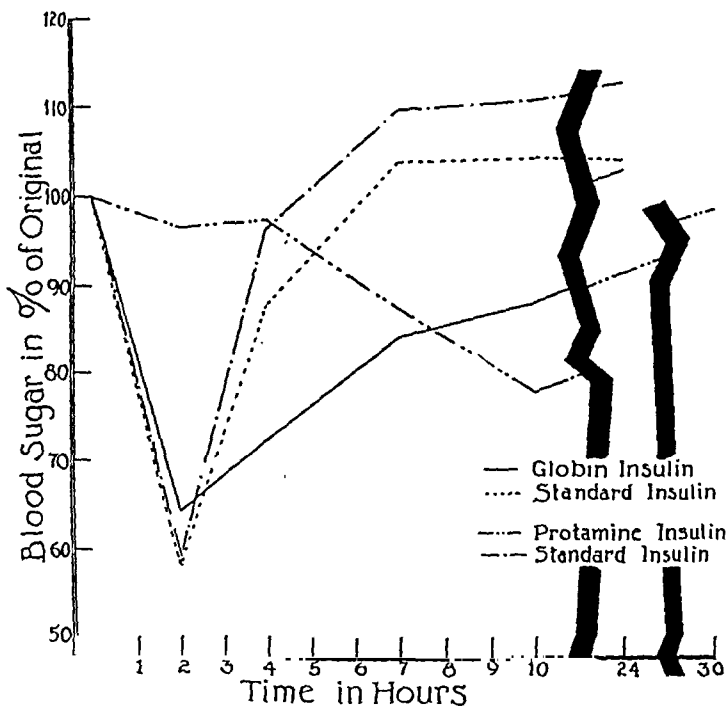


FIG. 2.—COMPARISON OF REGULAR, GLOBIN AND PROTAMINE INSULIN. Injections of 0.5 unit per kg. into each of 30 rabbits. After 1 week the experiment was crossed or reversed as in Figure 1. The effect of standard insulin is spent in 5 to 6 hours. The globin curve is similar to the standard for the first 2 hours; but the effect is noticeable for more than 10 and less than 24 hours. No effect is apparent for the first 4 hours after protamine injection. Maximum activity is delayed for more than 10 hours, and the blood sugar is still below the initial value after 24 hours.

The present communication is based on an experience with this preparation in 25 diabetic patients. A single injection was given 30 to 45 minutes before breakfast. The carbohydrate allotment was usually distributed in varying amounts for breakfast, lunch and dinner, depending on the effect of the insulin and severity of the diabetes. In this study our practice has been to administer the diet suitable to the age, weight and physical condition of the patient and then to adjust the insulin to this plane.

The urine sugar was determined in periods, or, in some cases, each voiding was tested with Benedict's solution. Blood sugars

were estimated as often as four times daily, that is, fasting, before lunch, before dinner, and at 10 P.M.

Whenever possible, periods of administration of the globin zinc insulin preparation were compared with protamine zinc insulin and also with standard insulin. Numerous difficulties are encountered in a comparison of this sort. It is not easy to get otherwise healthy diabetic patients to remain in the ward for a sufficient length of time to obtain adequate comparable periods. Interpretation is obscured

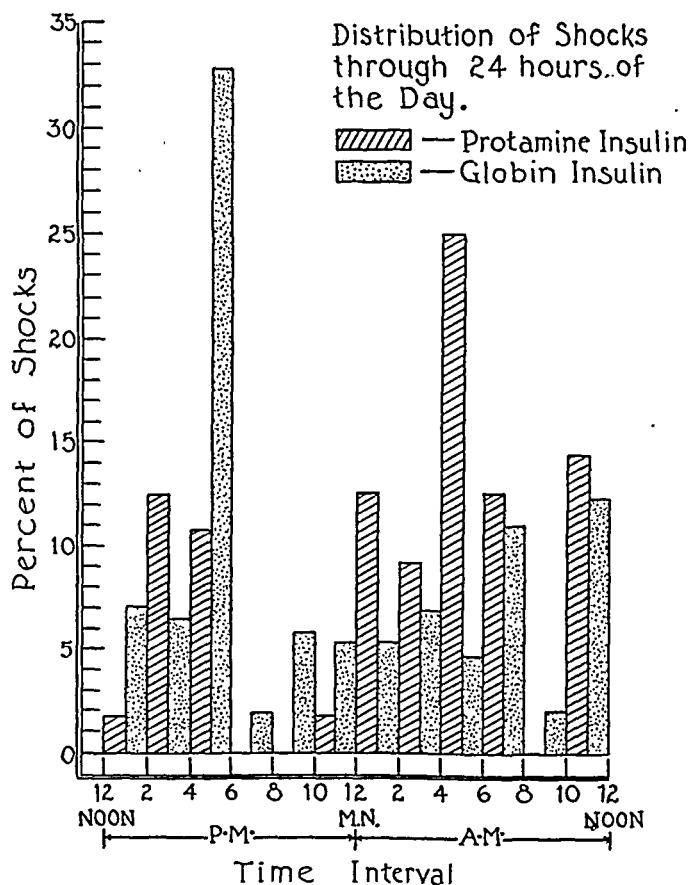


FIG. 3.—Distribution of shocks through 24 hours of the day.

by the cumulative tendency of protamine zinc insulin and by the occurrence of insulin shocks, which are almost unavoidable. In juvenile cases lack of uniform physical activity often confuses the comparison. In a number of instances we have observed what appears to be a temporary increase in the severity of the diabetes after insulin shock. This may be due to a decrease in the insulin-producing activity of the pancreas following the over-supply of the hormone. The bewildering fluctuations in sugar excretion so fre-

quently observed in juvenile patients, when diet and external conditions are apparently unchanged are difficult to explain. We really know little regarding the mechanism of insulin action. Glycogen mobilization and other ferments and coferments that participate in sugar oxidation may be limiting factors. These and other variables make judgment difficult and caution necessary.

TABLE 1.—CASE RECORD COMPARING EFFECTS OF REGULAR PROTAMINE AND GLOBIN INSULINS. Z. L., AGE 60 (HISTORY No. 508695).

		Data of Previous Admission.						
		Diet.			Insulin.			Regulation.
Dates, 1937.		C.	P.	F.	A.M.	M.	P.M.	
1/22-2/6	100	60	50	20	0	20 R	Good
2/6-2/13	100	60	50	30	0	0 P	Good
2/14-2/20	100	60	50	30	0	0 G	Excellent

		Blood sugars before.							
		Diet.			Break-fast.	Lunch.	Dinner.	10 P.M.	Urine sugars.
Dates, 1938.	Insulin.	C.	P.	F.					
7/16	40 P	120	60	50					Sugar free during entire period.
7/18	40 P				110	138	123	140	
7/28	40 G								
7/31	40 G							118	
8/1	40 G				104	117	72		
8/3	40 G								
8/8	40 G					132	133	126	
8/9	40 G				151				

Comment: Shows the similar effect of protamine and globin insulin on a mild diabetic who is on a low carbohydrate diet.

G = globulin insulin.

P = protamine zinc insulin.

R = regular or standard insulin.

TABLE 2.—CASE RECORD COMPARING EFFECTS OF PROTAMINE AND GLOBIN INSULINS. J. W., AGE 64 (HISTORY No. 465816).

Date.		Data of Previous Admission.										Regulation. Excellent					
		Diet.				Insulin.											
		C. 200	P. 70	F. 100	A.M. 10	M. 0	P.M. 10										
August, 1936																	
		Blood sugars before.							Urine sugars.								
						Breakfast.	Lunch.	Dinner.	10 P.M.	9 A.M.	11 A.M.	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	6 A.M.
Date, 1937.	Insulin	C.	Diet. P.	F.													
5/19	47 P	300	80	80	111	126	121	116	+-	+-	0	0	0				
5/20	36 G					159											
5/21	47 G				116	171	133	170									
5/24	47 G					121	123	125									
5/27	47 G	210	80	80	94	134	124	119	+-	0	+-	+-	+-	+-	3+		
5/28	47 G	296	80	80					+-	+-	+-	+-	+-	+-	+-	+-	+-
5/29	47 G	300	80	80					+-	+-	+-	+-	+-	+-	+-	+-	+-
6/4	47 G				94	116	91	121	+-	2+	0	+	+	+	+	+	+
6/7	47 P							116	+-	+-	+	+	+	+	+	+	+
6/8	47 P				94	123	154		+-	+-	+	+	+	+	+	+	+
6/14	47 P	294	80	80					+-	+-	+	+	+	+	+	+	+
6/15	47 P	300	80	80					+-	+-	+	+	+	+	+	+	+
6/18	47 P					109	110		+-	+-	+	+	+	+	+	+	+
6/21	47 P	300	70	80				183	0	0	+	+	+	+	+	+	+
6/22	47 P	300	66	80	326				0	0	+	+	+	+	+	+	+
6/23	47 P								0	0	+	+	+	+	+	+	+
6/24	47 P				112	156	200	218	+	+	+	+	+	+	+	+	+
6/26	47 P	300	70	80					0	0	+	+	+	+	+	+	+
6/27	47 P					169	166	172	0	0	+	+	+	+	+	+	+
6/28	35 P	200	76	115					0	0	+	+	+	+	+	+	+
6/29	35 P				148				0	+	+	+	+	+	+	+	+

Comment. If anything, better control on globin insulin.

G = globin

P = protamine zinc insulin

R = regular or standard insulin

Discussion of the Tables. We have used globin zinc insulin in children and adults for about 2 years. The maximum single dose was 145 units. Daily doses of 60 units or more have been injected for about 2 years without any apparently harmful effect. At present, water clear solutions are used.

If the usual morning dose is too large, a hypoglycemic reaction will occur usually in the late afternoon, that is, about 7 to 12 hours earlier than the average protamine shock period.

TABLE 3.—CASE RECORD COMPARING EFFECTS OF REGULAR PROTAMINE AND GLOBIN INSULIN. H. D., AGE 42 (HISTORY No. 354588). DIABETES DISCOVERED IN 1933.

<i>Data of Previous Admissions.</i>									
Dates.	Diet.			Insulin.			Regulation.		
	C.	P.	F.	A.M.	M.	P.M.			
9/17/33-9/27/33	100	60	50	30	0	18	Excellent		
4/30/37-5/13/37	250	75	100	44	0	22	Good		
5/17/37-5/17/37	250	75	100	40	0	40	Good		

Dates, 1937.	Insulin.	Diet.			Blood sugars before.				Urine sugars.		
		C.	P.	F.	Break-fast.	Lunch.	Dinner.	10 P.M.	11 A.M.	4 P.M.	7 A.M.
12/3	70 G	250	100	75							
12/7	70 G				149	309	233	229	○	+-	+-
12/8	70 G				148	322	204	274	○	○	+
12/10	85 G								○	○	○
12/11	85 G				104				○	○	○
12/13	85 G				71				○	○	○
12/14	82 G								○	○	○
12/15	82 G				67	145	118	96	○	○	○
12/16	82 G				110	172	106	95			

Comment. Since discharge about 11 months ago she has visited the clinic about 21 times. Regulation has been quite satisfactory.

G = globin.

P = protamine zinc insulin.

R = regular or standard insulin.

In certain cases, usually severe, and especially juvenile cases, the same unexplained daily variation in sugar excretion is encountered as when the regular or protamine preparations are used. The charts and other observations (omitted for lack of space) indicate that a single daily dose of globin insulin will regulate the mild and moderately severe cases. In those severe cases requiring 100 or more units daily, complete control was often impossible during the entire 24-hour period. Periods of hyper- and hypoglycemia may be unavoidable, but they often occur when several doses of standard insulin are used, and certainly when a single dose of protamine insulin is administered. However, we have encountered several cases, uncontrollable with protamine zinc insulin, which were regulated to greater satisfaction with single doses of 80 to 120 units of the globin compound.

Globin zinc insulin is less apt to produce shocks during the night than protamine zinc insulin (Fig. 3).

We sincerely believe that the behavior of globin zinc insulin warrants further trial by clinicians especially trained in the management of diabetic patients.

TABLE 4.—CASE RECORD COMPARING EFFECTS OF REGULAR, PROTAMINE AND GLOBIN INSULINS. R. H., AGE 19 (HISTORY No. 309995).

Data of Previous Admissions.																	
Date.		Diet.				Insulin (standard).				Regulation.							
October, 1931		248-100-20				10-0-3				Fair							
January, 1932		220-70-100				14-0-7				Fair							
Seen in Out-Patient Department until admitted July, 1933		200-70-100				55-0-20				Poor Fair							
Followed in the Out-Patient Department until the admission recorded below. Patient's urine has almost always showed large quantities of sugar even when receiving 65-0-25 units of insulin (Standard).																	
Date, 1939.		Insulin.		Diet. C. P. F.		Blood sugars before.				Urine sugars.							
						Breakfast.	Lunch.	Dinner.	10 P.M.	9 A.M.	11 A.M.	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	6 A.M.
2/2	20 S 45 P	}	180	80	80	286					4+	2+	0	0	0	0	4+
2/9	30 S 60 P		180	80	80			115		4+	2+	0	0	0	0	2+	+
2/10	30 S 60 P	}	180	80	80	200				+	0	0	0	0	0	+	0
2/11	30 S 60 P		200	80	80					+	0	0	0	0	0	0	0
2/13	30 S 60 P	}	250	80	80					0	0	0	2+	+	+	+	0
2/14	30 S 70 P		250	80	80					0	0	0	+	0	2+	4+	2+
2/16	15 S 70 P	}	250	80	80	111	59	54	78	2+	+	0	0	0	+	0	0
2/21	85 P		250	80	80					+	3+	4+	4+	4+	3+	4+	2+
2/22	85 P	}	250	80	80					+	2+	2+	4+	+	0	0	0
2/23	85 P*		250	80	80	48				+	3+	4+	4+	3+	0	0	0
2/24	85 P	}	250	80	80					0	+	+	3+	0	0	4+	3+
2/25	85 P		250	80	80					+	0	+	4+	4+	2+	4+	3+
2/26	85 P	}	250	80	80					+	0	0	0	0	0	0	0
2/27	85 P		250	80	80	100	179	160		0	3+	3+	4+	3+	2+	3+	4+
2/28	85 G	}	250	80	80					3+	3+	+	0	0	0	0	0
3/1	85 G		250	80	80					0	0	0	0	0	0	0	0
3/2	85 G	}	250	80	80					0	0	0	0	0	0	0	0
3/3	75 G†		250	80	80			82	144	0	0	0	0	0	0	+	0
3/4	75 G	}	250	80	80	108	177			0	0	0	0	0	0	+	0
3/5	75 G		250	80	80					0	0	0	+	0	0	0	0
3/6	75 G	}	250	80	80					+	2+	3+	3+	2+	2+	2+	+
3/7	75 G		250	80	80			44	89	+	+	0	0	0	0	0	0
3/8	75 G	}	250	80	80	74	55			0	0	0	0	0	0	0	0

* Hypoglycemic shocks at 11 P.M., 2 A.M., 6:35 A.M.

† Hypoglycemic shock at 5 P.M.

Comment: The regulation of this patient was fairly satisfactory on a double dose of standard and protamine insulin. On a single dose of insulin, however, the regulation was better with globin than protamine insulin. Patient discharged on 65 units of globin insulin.

G = globin

P = protamine zinc insulin

R = regular or standard insulin.

Summary. The effect of a single daily dose of a clear solution of globin insulin was studied in about 25 cases of diabetes in a period of about 2 years.

1. No skin reactions were observed.
2. Mild and moderately severe cases were adequately controlled.
3. Several cases uncontrollable with protamine zinc insulin were controlled fairly well with the globin compound.

The coöperation of Drs. Edgar Stillman, Bertram J. Sanger, Henry E. Marks and Rudolph Scharf of the Metabolism Service of the Presbyterian Hospital is gratefully acknowledged.

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PREDICTION AND PREVENTION OF LATE PREGNANCY ACCIDENTS IN DIABETES.

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THE problem of pregnancy complicating diabetes has been of great interest to us, for unlike other complicating diabetic situations the continued use of insulin did not solve it. Until recently it has been nearly as true of the insulin as of the pre-insulin era that only every other diabetic pregnancy terminated successfully. The accidents common in diabetic pregnancies do not concern the welfare of the mother, for maternal mortality is and should be low, but do concern the welfare of the child destroyed, by: 1, early spontaneous abortion, miscarriage or premature birth; 2, stillbirth; and, 3, a neonatal type of death common within 24 hours of delivery.

This statement is based upon a study of the records of 353 pregnancies in 242 diabetic women who have been under our care since 1898. The number includes patients who were treated by us during pregnancy and also those patients who were treated elsewhere during this period and consulted us at some later date. Excessive fetal mortality rates have been reported by all authors of obstetrical diabetic literature. Even when we confine our studies to reports of the year 1938 when we would expect to find the benefit of most modern treatment of diabetes, discouragingly high fetal mortality rates are reported by Johnstone,⁷ Potter and Adair,¹¹ Brandstrup and Okkels,² and Herrick and Tillman.⁵

From Table 1, in which are tabulated all cases with known outcome in the pre-insulin and insulin eras, it is evident that excluding surgically interrupted pregnancies the fetal mortality in the pre-insulin era was 44% and in the insulin era 38%. In the pre-insulin era, early and late fetal deaths occurred with equal frequency. In the insulin era, 60% of the fetal deaths were late, due to stillbirth or neonatal accidents and 40% to spontaneous abortions. The prob-

lems are therefore of nearly equal importance, but the late pregnancy accidents lend themselves to study whereas the early ones do not. This is true because so often the patient early in pregnancy reports for medical care only after incomplete abortion. For this reason, it has been our chief concern to investigate the cause and the means to prevent late accidents of diabetic pregnancies.

TABLE 1.—OUTCOME OF 353 PREGNANCIES IN 242 DIABETIC WOMEN.
(Analysis based on histories as well as experience of George F. Baker Clinic.)

Era.	Total No.	Live births.	Neo-natal deaths.	Still-births.	Abortion or miscarriage.	Therapeutic abortion.
Pre-insulin	108	57	0*	23	23	5
Insulin	245	142	24	27	35	17

* Undoubtedly neonatal deaths occurred in the pre-insulin era. The data based on records going back to 1898 and based on case histories cannot be as accurate as more recent ones and those based on actual experience.

For years, and quite naturally, too, the authors of obstetrical diabetic literature have attributed these accidents to diabetes *per se*, its complications or its treatment. As a longer interval of time has passed we have not been able to agree with the opinion that the accidents of diabetic pregnancies are caused by faulty management of the disease, diabetes, nor can we agree with the opinion that they can be prevented by adequate control of the diabetes. We have seen that severe diabetic crises—coma and hypoglycemia—are not at all incompatible with the birth of a living child. Thus among 14 accidents in late pregnancy, maternal coma occurred only twice, in each instance precipitated by infection, and the remaining 12 patients had no signs of acidosis. These latter had taken meticulous care of their diabetes to insure the birth of a living child. In contrast to this experience other patients careless of the diabetic routine have had successful outcome of the pregnancy. For this reason we have been stimulated to search for some extradiabetic factor common in diabetic pregnancies.

The first suggestion of a possible hormonal imbalance in diabetic pregnancies was made in 1933 by Murphy¹⁰ who reported that the prolan excretion of 2 diabetic women exceeded the normal. This work was carried much further by Smith and Smith^{12a,b} who, evaluating the problem of hormones in pre-eclamptic toxemia of pregnancy, quite naturally turned to our diabetics in order that they might study the problem from early to late pregnancy since the incidence of toxemia in diabetes was known to be great. They had observed that an excess of serum prolan (anterior pituitary-like substances) precedes and predicts pre-eclamptic toxemia. These observations were confirmed in the toxic diabetic.

But along with these very important biochemical observations, equally important clinical correlations became evident to us; first, that stillbirth, the most dreaded accident in diabetic pregnancies, was not related to diabetes or its specific complication, coma, but was definitely related to pre-eclamptic toxemia and as time elapsed that the accidents—neonatal death and premature delivery—were also related to the abnormal hormone picture. The relationship of toxemia and stillbirth first became apparent to us when, in order to obtain specimens for biochemical research, the patient reported to us at almost daily intervals. We then observed that in many diabetic women the course of pregnancy was uneventful until the sixth month; at any time thereafter, that the patient often developed edema, albuminuria and a rising blood pressure. Early in our experience we found that shortly after the rise of the blood pressure the fetus died and thereupon the signs of toxemia promptly disappeared. The entire clinical picture can occur and disappear in as short a period of time as 1 week, but we now know is predicted some 4 to 6 weeks by the rise of the serum prolان.

Between January, 1936, and March, 1939, 35 completed pregnancy cases have been studied with examinations for serum prolان. At first, as a part of the studies by Smith and Smith, later because we were convinced of its value, we adopted it as a routine laboratory procedure.

Method. The laboratory procedure as worked out on a routine basis is as follows: Beginning with the 24th week of pregnancy or as near that time as can be calculated by the irregular data of the patient, determinations of serum prolان are made each week or each 5 days if indicated by high results. The serum is precipitated with alcohol, the precipitate is extracted with ether which removes the estrin and the remaining precipitate is taken up in suspension with 6 cc. of normal saline. One cubic centimeter of the saline suspension is injected twice a day for 3 days into immature female white rats 21 to 23 days old weighing 30 to 35 gm. On the fifth day after the initial injection the ovaries are examined. A positive test is indicated by the presence of corpora lutea. The results are recorded in terms of "rat units." The prolان present in 1 cc. of serum is considered as 100 rat units per 100 cc. of blood; 0.5 cc. equals 200 rat units.

Our routine procedure consists of running duplicate tests for 200 R. U. If positive findings result from injection of 0.5 cc. of serum, the test is repeated using smaller amounts of serum.

The details of the biochemical research, the relationship of this problem to pre-eclamptic toxemia, will be reported by Smith and Smith. It is our purpose here to summarize the clinical course of the patients studied and to give the coincidental condition of the child; second, to present evidence that this laboratory test predicts the accidents common in diabetic pregnancies, and, third, to summarize the end-results of patients treated with replacement estrin and progestin therapy.

The 35 patients studied may be logically divided into 4 groups: first, 14 patients whose values for serum prolان were repeatedly normal (namely, less than 200 rat units per 100 cc. of blood from

the 6th to the 8th month); 10 patients whose values for serum prolan were supernormal and which rose steadily to term; 2 cases whose values were supernormal but which fell steadily; and 9 patients whose values were supernormal but who received replacement therapy. In Table 2 the 35 patients are classified according to the highest late prolan values. In addition, the average blood sugar and insulin are listed according to each trimester; also, the values for carbon dioxide combining power, and the lowest value for plasma protein. Data on the clinical signs of toxemia, duration and outcome of the pregnancy and the type of delivery are also included.

Of the 35 patients carefully studied, 9 were former juveniles—patients with onset of diabetes under 15 years of age. Only one had onset of diabetes during pregnancy and only one required no insulin. Twenty-six had severe or moderately severe diabetes. One patient developed coma, one had a 3-day interval of hypoglycemia following the mistaken administration of 276 units of protamine zinc insulin. In general, the control of diabetes was good in all patients.

Clinical Course of the Pregnancy. The clinical course of the 14 patients whose values for serum prolan were repeatedly normal was completely uneventful. None developed toxemia, none miscarried. Quite different was the clinical course of the 10 patients whose values for serum prolan were supernormal and who received no therapy. All developed complications. Seven developed toxemia. The remaining 3 delivered themselves prematurely. All toxemic patients were hospitalized, treated with rest, low-salt, high-protein diets and supplementary vitamin B and calcium, yet progressive toxemia was the rule.

Of greatest interest to us was the clinical course and biochemical behavior of the 2 cases—successive pregnancies in the same patient whose values for prolan fell. This fall of prolan was preceded by a rise of estrin which was noted some 4 weeks prior to the normally expected time. During the first^{12c} pregnancy she developed well marked signs of toxemia which decreased in severity with the fall of prolan. Less well defined signs in the second pregnancy disappeared entirely. The biochemical behavior of this patient gave further presumptive evidence of the probable value of estrin therapy.

On the advice of Smith and Smith the next group of patients, whose values for serum prolan were supernormal, received massive doses of estrin, 150,000 to 300,000 international units as progynon B and in addition progestin, in the form of 10 to 20 mg. of proluton daily* (in a few instances testosterone was substituted for progestin). The rationale for progestin therapy^{12d} is substantiated by the demonstration of a lowered excretion of sodium pregnandial glucuronidate. Brown, Henry and Venning³ have also found low estrin and diminished pregnandial excretion in pregnancy toxemia. Weil¹⁵ has also reported lowered pregnandial excretion in toxemia.

* Progynon B and Proluton were supplied to us through the courtesy of the Schering Corporation.

16	2	3714	5.1	0	+	280	130/80	+	500	?	S.B.	N
17	5	2614	5.1	4	+	400	180/100	+	333	37	L.B.	0	+	4.8	N
18	21	31	.10	.11	.15	.58	47	23	+	60	118/70	130/80	150/110	+	333	36	L.B.	0	0	6.2	C
19	4	25	..	.15	.11	47	6.0	+	80	..	120/80	120/80	+	333	37	L.B.	0	0	7.7	C
20	17	25	.11	.16	.17	.74	38	12	+	50	110/60	100/70	140/80	+	333	37	L.B.	0	0	6.9	C
21	10	23	..	.12	.17	.50	31	14	+	50	..	110/80	120/80	+	333	37	L.B.	+	+	7.2	C
IV.																								
22	6	18	.15	.08	.15	.60	50	..	13	0	10	130/80	120/90	0	50	..	L.B.	0	+	7.4	C
23	8	20	.10	.16	.13	.46	49	5.0	+	v.s.t.	130/80	100/60	120/80	0	100	..	L.B.	0	0	6.8	C
24	4	36	.09	.09	.10	0	23	+	0	100/70	120/80	120/80	100/80	0	<200	37	L.B.	0	0	7.8	N
25	16	25	..	.14	.13	25	+	s.p.t.	..	110/80	120/80	0	150	..	L.B.	+	+	6.4	C
26	4	32	.12	.21	.17	.36	48	39	0	s.p.t.	120/70	120/80	90/60	0	100	38	L.B.	+	0	7.0	C
27	6	21	..	.15	.09	6.4	8	0	s.p.t.	..	120/60	124/80	0	<200	..	L.B.	0	0	7.5	C
28	4	23	.17	.18	.13	.42	31	+	30	120/80	120/80	120/80	0	100	35	L.B.	+	+	8.8	C
29	7	28	.12	.12	.15	.32	45	10	+	s.p.t.	..	110/60	112/78	0	150	36	L.B.	0	+	5.0	C
30	31	31	..	.17	.11	41	5.6	+	80	..	104/70	110/80	0	100	38	L.B.	+	+	8.3	C
31	7	37	.29	.19	.13	.60	45	40	+	30	130/70	120/80	150/80+	0	100	38	L.B.	0	0	10.6	N
32	3	37	.17	.18	.13	.25	52	..	+	10	120/80	160/110	150/90	0	100	34	N.N.	+	+	8.0	C
33	.5	36	..	.17	.19	.20	41	44	+	50	..	140/80	170/120	0	100	..	L.B.	0	+	6.9	N
34	9	38	.11	.19	.10	.28	47	44	+	15	140/80	140/80	170/80	0	50	37	L.B.	0	0	8.8	N
35	5	32	.25	.22	.15	.40	37	48	+	0	120/80	110/80	120/80	0	<200	39	L.B.	0	0	8.4	N

* Coma.

† Pvelitis.

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culosis and pvelitis.

+ One reading only.

Comparison of the clinical course of patients whose values for serum prolactin were:

(1) supernormal untreated; (2) supernormal self corrected; (3) supernormal treated with replacement therapy; (4) normal.

L.B. = Live birth.

S.B. = Stillbirth.

N.N. = Neonatal.

C. = Cesarean section.

N. = Normal delivery.

Sp. = Spontaneous premature delivery.

The purpose of this therapy was twofold: Prevention as well as correction. For this reason, patients so treated include those whose values for prolan were repeatedly supernormal and who had developed all signs of toxemia and those with few suggestive signs. Thus of the 9 patients 4 had hypertension, albuminuria, edema, pain, headache, or nausea and vomiting. One patient had all signs and symptoms except hypertension; 3 had albuminuria and edema and one edema only.

Replacement therapy was followed by a drop in serum prolan controlled by the size and frequency of the dose of hormones. No instance of progressive toxemia occurred. Not one miscarried. There was a tendency for the serum protein which fell to low levels to rise without change in diet, the weight to fall, the urinary output to be increased, the albumin to be diminished and the blood pressure to fall.

Fetal Mortality. Of greater importance in our diabetic problem, however, is the apparent effect of the abnormal hormone picture, upon the child. Fetal deaths in this group of 35 patients occurred with one exception among the patients whose values for serum prolan were supernormal. Thus among our 14 infants of mothers whose values were normal there was 1 death (7%). This death occurred 2 hours after delivery and was classed as asphyxia pallida. The autopsy was negative. A strong lethal factor was suspected, because there was not only maternal diabetes but grandmaternal diabetes on both sides of the family.

In contrast to the low mortality rate of 7% in infants of diabetic mothers whose values for serum prolan were normal, is the high rate of 60%; 6 of the 10 infants, whose mothers' prolan values rose steadily to term. These deaths occurred three times in relation to toxemia and three times in relation to premature delivery. The positive findings at autopsy were hemorrhage into the adrenal, once, in the only infant who survived toxemia; erythroblastosis among the premature infants, once; inanition once and hematopoiesis of the liver once. The remaining 2 infants were macerated.

In contrast to the high fetal mortality in the group of patients whose values for serum prolan were supernormal and who received no therapy, was the low mortality of those who received replacement estrin and progestin therapy (150,000 to 300,000 international units of estrin, 10 to 20 mg. progestin per day). Eight of the 9 had successful outcome. Because of the high cost of treatment under usual conditions, we reduced therapy in the ninth patient after the prolan had reached normal values. A typical intra-uterine fetal death followed after a rise of prolan.

As a control the past obstetrical histories of these patients are of interest, because in diabetes the pattern of the pregnancy is usually repeated. Four of the 9 were primiparæ, 3 were known and 1 suspected previously to have had toxemia, all with stillbirths. In addition, 2 had miscarried. The only patient who had a living

child previously was the one whose therapy was reduced and finally omitted. The living child had been born 4 years prior to the onset of her diabetes. The most remarkable patient in the group was Case 1469, whose diabetes was of 21 years' duration and who had hemorrhages and exudate of the retina with clinical signs of toxemia. These signs disappeared after 1 week's therapy.

In addition to the 35 cases whose serum prolans have been studied, 21 late pregnancy cases were followed and delivered by us. Of the 22 infants (one twin pregnancy), 16 survived. Three of the deaths occurred *in utero* and 3 on the first day of life. Of the stillbirths 2 occurred in well controlled cases; 1 in a patient who developed coma during labor but since the fetus was born macerated, we believe it died prior to the coma. Of the 3 neonatal deaths 1 occurred at 24 weeks during severe lobar pneumonia and mild diabetic coma.

In addition to a high mortality rate, the infants of diabetic mothers are predisposed to asphyxia, gigantism, congenital defects and hypoglycemia.

Congenital Defects. In this small group of 35 patients, congenital defects occurred 3 times. One child had a club foot, claw hand, web toes and missing fingers and in addition is probably feeble-minded; another had a congenital heart lesion and a third congenital luxation of both hip joints. All occurred in the abnormal hormone group, 2 among patients who received treatment.

Hypoglycemia. Hypoglycemia occurs, but in our experience it has never been a fatal accident. Blood sugar studies (127) have been done on 38 infants; 40 were 60 mg. or less—of these 20 were 60, 10 were 50, 3 were 40, 6 were 30, and 1 was 9 mg. Of the 38 patients, 7 had one determination for blood sugar only. Of the 31 patients with repeated tests, 21 had values less than 70 mg., 23 received no glucose, 15 received glucose. Clinical signs of hypoglycemia were encountered once. Infants of diabetic mothers do have hyperplastic islands, but stabilization of the sugar in the blood occurs on the second or third day and hypoglycemia may be related to maternal insulin. There was no correlation between hypoglycemia and prolan values.

The level of the blood sugar of newborn infants was studied by Kitteringham and Austin⁸ who found, using the modified Folin-Malmos technique, that the level of the blood sugar of normal infants varies from 55 to 75 mg. on the first 2 days and reaches higher levels on the third. A drop of blood sugar level occurs within 3 to 6 hours after birth. This experience is similar to that found in the infants of diabetic mothers. Thus only 10 of the blood sugars out of our 127 determinations, or a total of 9 infants out of 38, had levels of blood sugar lower than infants of normal mothers. McKittrick⁹ studied infants of normal mothers and came to similar conclusions. His lowest value was 28 mg. in an infant whose behavior was entirely normal.

Asphyxia. Asphyxia in its fatal form, with 1 exception, occurred in infants whose mothers' values for serum prolactin were supernormal.

Gigantism. Gigantism or "over-ripeness" has been reported as characteristic of infants of diabetic mothers. Of 91 infants in our series 42 weighed more than 8 lbs. and 22 weighed less than 7 lbs. Authors of obstetrical diabetic literature have attributed the large size to hyperglycemia. This tendency for gigantism, however, may be related to abnormal hormone picture in that weights appear to be controlled in the treated group and this is further suggested by the independent experiments of Teele, Snyder and Hoopes^{6,13a,b,14} who have injected prolactin into pregnant rats and rabbits and have produced a result not unlike a diabetic pregnancy, miscarriage, still-birth overdevelopment, death and maceration of the giant fetus! Snyder^{13b} has shown by the intravenous injection of prolactin into rabbits in the last quarter of pregnancy that when a new set of corpora lutea were induced on the 25th day a premature separation of the placenta occurred in certain implantations whereas those adjacent were still adherent and destined to persist 9 days post-term. He thinks that edema and actual endometrial growth associated with the development of a new set of corpora cause sufficient structural changes in some of the placentae to dislodge them. Such dislodgment is always associated with uterine bleeding. The young may be born alive. In like manner, Bøe¹ showed prolongation of pregnancy with fetal weight increase in rats. Hypophysectomy produced the same prolongation in some instances with striking increase in fetal weight. But weight increase cannot be explained on the basis of prolongation of pregnancy for mechanical obstruction by ligation of uterine horns did not cause an increase in fetal weight. In his analysis of uterus, fetus and placenta during prolonged gestation, he reaches the conclusion that the fetal death resulted from failure of the placenta.

The relative size of the infants in our series is shown in Table 3. Since we have elected premature delivery in many cases we have undoubtedly lowered average weights somewhat. The greatest relative average weight was 7.1 lbs. in the 33d week among the supernormal prolactin untreated cases. The lowest relative and absolute average weight occurred in the group of patients whose values for prolactin were supernormal but who received hormone therapy, namely, 6.8 lbs. in the 36.5th week of pregnancy. The effect of prolonged high estrone dosage on impaired body growth was first shown by Zondek.¹⁶

Discussion and Summary. No attempt to explain the mechanism of the abnormal hormone picture in diabetic pregnancies is made here. Before determinations for prolactin were routinely done in our clinic, the pregnant diabetic was a nightmare to us, for we never knew by severity, duration, age or control of diabetes which patient might be expected to progress satisfactorily and which might be expected to miscarry or have an intra-uterine death. The test for

prolan permits us to classify the patients according to hazard and to gauge the effect of therapy.

TABLE 3.—COMPARISON OF THE OUTCOME OF DIABETIC PREGNANCIES IN (a) PATIENTS WHOSE SERUM PROLANs WERE NOT STUDIED; (b) THOSE WHOSE VALUES WERE NORMAL; (c) SUPERNORMAL UNTREATED; (d) SUPERNORMAL TREATED.

	No. of cases.	Dur. of diab. av.	Age preg., av.	Bl. sugar, mg. %, trimester.			Insulin, units, trimester.			CO ₂ combining power, vol. %, trimester.			Wt. gain lbs.	Preg. dur., wks.	Baby's wt., lbs.	Live births.	
				1.	2.	3.	1.	2.	3.	1.	2.	3.				No.	%
(a) No prolan data* Control group Consecutive cases	20 (1 twin)	5.0	29	.14	.17	.16	25	40	30	33	23	38	26	37	7.7	16	76
(b) Normal prolan	14	6.0	30	.15	.16	.13	38	40	52	40	45	45	21	37	7.6	13	93
(c) Supernormal prolan Untreated†	10	5.8	28	.15	.16	.17	37	39	47	48	41	40	27	33	7.1	4	40
(d) Supernormal prolan Treated	9	9.0	28	.12	.15	.15	55	57	74	49	44	41	15	36.5	6.8	8	90

* Excluded 2 for inadequate data.

† Excluded 2—self corrected.

Out of 14 patients whose values for serum prolan were normal, none developed pre-eclamptic toxemia, none miscarried and there was one fetal fatality. Out of 10 patients whose values were hyper-normal and who received no therapy, 7 developed toxemia, 3 miscarried and there were 6 fetal fatalities. Except for subsiding toxemia the 2 instances of self corrected hyper-prolanemia were uneventful. Out of the 9 treated cases, 8 had toxemia which subsided, none miscarried and there was one needless fetal death, the case where therapy was omitted.

TABLE 4.—UNFAVORABLE OUTCOME. (NUMBER AND TYPE.)

Year.	No. of cases.	Still-birth.	Neonatal death.	Total, %.	Delivery, type.	
					Cesarean.	Normal.
1925-31	12	2	1	25	3	9
1932-35	13	2	3	38	8	5
1936-37	16	1	4	31	11	5
1938-39	17	1	0	6	11	6

The effect of our knowledge and therapy upon the outcome of diabetic pregnancies is shown in a comparison of cases by years. Long familiar with the late intra-uterine death of the fetus but before the present concept of endocrine imbalance, premature delivery by Cesarean section was elected. By this procedure alone there was no favorable effect upon the outcome of the pregnancy, as shown by the almost constant rate of fetal deaths up to the year 1938. The result of estrin and progestin therapy is reflected by the drop from 30 to 6% mortality in our 1938 to 1939 experience. As we gain confidence, the number of Cesarean sections will probably be reduced.

The technique for the test is relatively simple, but the cost of therapy great. However, present experience seems to indicate that inexpensive, oral preparations of synthetic estrogens, namely, DAES,⁴ may also prove of value in the treatment of these patients.

Conclusions. Accidents of diabetic pregnancies in 35 consecutive cases studied for serum prolactin values from 1936 to 1939 were not related to control of diabetes or its specific complication, coma. With one exception, stillbirth, neonatal deaths and miscarriage occurred among those patients whose values for serum prolactin were super-normal. Hypoglycemia and congenital defects in this series were not fatal accidents. Against the abnormal hormonal balance measured by the serum prolactin, the diabetic woman appears to have a good defensive mechanism, destroying the offending placenta and incidentally the child, accounting for the high incidence of stillbirth, or expelling the placenta and the child, accounting for the high incidence of miscarriage. Replacement estrin and progestin therapy in a small group of patients was followed by the restoration of the normal value for serum prolactin and the successful outcome of the pregnancy.

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ERYTHROPOIESIS FOLLOWING BLEEDING PEPTIC ULCER.

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HEMORRHAGE is the most common major complication of peptic ulcer, yet despite its importance and frequency there still exists a wide variety of opinion regarding the problems of its prognosis,

course and treatment. The literature has dealt mainly with the problem of the emergency resulting from the hemorrhage. Very little information has been reported concerning the course and the prognosis of the patients who survive the acute episode.

The present paper, based on the records of 237 admissions to this hospital of patients with peptic ulcer, is an attempt to aid in the evaluation of the problems presented by the anemia that follows the bleeding. Special attention has been given to the symptoms resulting from the hemorrhage and the rate of recovery of the red blood cells after the bleeding episode.

All admissions from 1913 to 1936 were included that satisfied the following criteria: 1, Roentgen ray or postmortem evidence of peptic ulcer or a clinical diagnosis of a peptic ulcer based on a typical long standing symptomatology; and, 2, a definite history of melena or hematemesis either within a month before entry or during the hospital stay.

Sex and Age. The group comprised 46 females and 191 males ranging in age from 12 to 80 years. Of the males 47% were from 40 to 59 years while only 34% were below 40. This agrees essentially with the figures for age distribution found in other series.^{3,5,8a} In the relatively small group of females, however, the age distribution was slightly different, 50% being below 40 years of age.

Location. The site of the lesion was definitely determined in a surprisingly large number of these cases, 204 of the 237 studied. Of these, 77% were duodenal, 14% gastric and the remainder either gastric and duodenal combined or jejunal.

Symptoms. Detailed accounts of the symptoms of the bleeding episode were obtained in 175 cases. The most common initial symptom was melena, which was noted in 54 cases. Evidence of exacerbation of the activity of the ulcer prior to bleeding usually was not present. Only 47 patients complained of increased pain, nausea, vomiting or epigastric distress before the hemorrhage occurred.

In a large group of patients (42 of the 175) the first suggestion of bleeding were the complaints of weakness coming on rather rapidly, syncope or dyspnea. These symptoms, resulting from the anemia or sudden loss of blood volume, preceded the tangible evidence of bleeding by 2 to 4 days in several cases. In addition to this group, 23 of the cases with exacerbation of activity of the ulcer as the first symptom of the bleeding episode presented the symptoms of blood loss mentioned above before either hematemesis or melena were noted. From this it seems that over one-third of the cases have symptoms resulting from blood loss as the first indication that a hemorrhage has taken place. Complaints of weakness of rapid onset in a patient with an ulcer history should suggest at once a bleeding episode despite the absence of other evidence of bleeding (*i. e.*, hematemesis or melena).

Hematemesis, though a common symptom later in the course of the bleeding episode, was not very frequently the initial complaint, only 32 out of 175 cases. It was an initial symptom in gastric ulcers slightly more frequently than in duodenal ulcers.

Syncope was one of the early symptoms of the bleeding episode that occurred in a fairly large proportion of the cases. It developed in 54 of the 237 cases, and in 21 of these it appeared before any tangible evidence of bleeding was noted. In 11 cases it was the initial event. Apparently the severity of the anemia at the time had no strict relationship to the appearance of syncope, for 32 of the cases had red blood cell counts on admission greater than 3 million. It seems more probably related to the vasomotor instability of the individual and the sudden blood loss. Though it occurred with slightly greater frequency in the older age groups, 41% of the cases were under 40 years of age, and of these one-half had admission red blood cell counts above 3 million. Thus it appears that the presence of syncope by no means indicates an especially severe hemorrhage either in a young or an old individual. It is also evident that syncope like weakness may be the first indication of a hemorrhaging ulcer.

Duration of the Ulcer Symptoms Before Hemorrhage. In an effort to determine if there was any relationship between the chronicity of the ulcer and the bleeding episode, the duration of the ulcer symptoms prior to the bleeding episode was noted in all cases. It was interesting to find that in each decade between 20 and 60 years of age 25 to 30% of the patients had had symptoms for less than 1 year. About 21% of the cases over 60 years had had symptoms for less than 1 year. About 30% of the individuals in each decade over 30 years had had ulcer symptoms more than 8 years. It seems apparent that neither the age of the individual nor the chronicity of the ulcer are important factors in the production of the bleeding episode.

Severity of Hemorrhage. While appreciating the difficulties in determining the severity of the hemorrhage, it seemed that the lowest red blood cell count was the best available measure. Consequently cases were grouped in 5 classes depending on the degree of anemia as determined by the lowest red blood cell count. Twenty-six per cent of the cases had a lowest red blood cell count between 1 and 2 million, 33% between 2 and 3 million, 25% between 3 and 4 million, 13% between 4 and 5 million and 3% above 5 million. The large proportion of severe hemorrhages is in accordance with the fact that only those cases were considered which had had a definite episode of hematemesis or melena. The severity of the hemorrhage appeared to be quite independent of the age or sex of the individual or the duration of symptoms of the ulcer.

Duration of Hemorrhage. In describing the bleeding episode, the duration of the hemorrhage is of importance. However, no attempt has been made to study that in the present paper since it is not possible to determine it accurately. Even in cases of hematemesis

it seems a somewhat unwarranted assumption to postulate an abrupt onset of hemorrhage, while in cases of melena the onset may clearly have been insidious. As for the cessation of bleeding, Hesser's work^{7a} indicates that this precedes the disappearance of occult blood from the stools by many days in a considerable number of cases.

Treatment. The great majority of the cases in this series (172 cases) were treated medically on a regimen approximating that proposed by Sippy^{16a,b*}. Thirty-six cases, chiefly in the early years of the hospital, were treated on a soft solid diet without alkali, and 29 cases were operated on during their hospital stay.

Previous Hemorrhages. Sixty-eight cases (28%) had had one or more previous hemorrhages, 43 cases had had one earlier bleeding episode, 13 cases had had two, and an equal number three or more. Age appeared to have no relation to the number of previous hemorrhages.

Dietary histories were not sufficiently specific to permit a detailed analysis of diet as a factor in the problem of repeated hemorrhage.

Recurrences. There were 5 cases with a recurrence of bleeding sufficient to give either hematemesis or melena during the hospital stay. One of these was a case of definite perforation, well walled-off, 3 were deeply penetrating ulcers, and the last, a gastro-jejunal ulcer. Recurrence of massive hemorrhage under treatment thus is seen to be rare, and when it does occur, should suggest the possibility of penetration or perforation.

Convalescence. Barring continued hemorrhage or other untoward complications, which are rare, the subsequent course of these patients is determined by two main factors: 1, the control of the symptoms of the ulcer; and 2, the control of the symptoms of the anemia, which after the acute phase is dependent principally on the rapidity of the hematopoiesis.

It has been demonstrated that the Sippy régime, conscientiously followed, is highly efficient in controlling the symptoms of uncomplicated peptic ulcer.⁴ As far as could be determined from the record, this régime was equally efficient in controlling symptoms of pain, nausea, bitter eructations and epigastric distress in patients who had bled recently.

The second factor in the course of these patients is the regeneration of the blood lost by the hemorrhage. Because it has been suggested that the alkali régime fails to promote as rapid regeneration as other methods of treatment,¹⁰ an analysis of the rate of erythropoiesis was made in these cases.

* Bleeding peptic ulcer has been treated routinely by alkali therapy since 1918. The majority were treated as follows: In the first 24 hours an initial dose of MgO followed by CaCO_3 2 gm. every $\frac{1}{4}$ hour for 10 hours; in the second 24 hours CaCO_3 1.3 gm. every $\frac{1}{2}$ hour during the day and 2.6 gm. every hour at night if patient is awake; in the third 24 hours 30 cc. of milk and cream every hour with Sippy powder No. 2 every $\frac{1}{2}$ hour. Thereafter the progressive Sippy régime is followed as usual without aspirations.

In the course of the hospital's history three standard methods of hemoglobin determination have been used at various times; Talqvist, Dare and Sahli. Because of the difficulty in comparing values obtained by three different methods it was considered impracticable to evaluate the rate of hemoglobin regeneration, and attention was concentrated on erythropoiesis.

Following the method of Schiødt^{15b} the erythropoiesis was expressed as the average daily increment calculated week by week from the date of the lowest red blood cell count. This was done for 177 cases in which such data were available. Transfused cases were separately considered. Cases were grouped on the basis of the lowest red blood cell count, 25% being in the group between 1 and 2 million (average lowest red blood cell count 1.6 million), 40% in the 2 to 3 million group (average lowest red blood cell count 2.7 million) and 28% in the 3 to 4 million group (average lowest red blood cell count 3.4 million). The remaining 7% had lowest red blood cell counts greater than 4 million.

Table 1 shows the average daily erythropoiesis week by week for each of the three principal groups.

TABLE 1.—AVERAGE DAILY ERYTHROPOIESIS.*

	1st week.		2d week.		3d week.		4th week.		5th week.		6th week.	
	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.	No. cases.	RBC rise.
1 to 2 million	45	115.0	42	60.5	39	53.9	30	73.0	21	35.8	8	69.5
2 to 3 million	71	80.5	61	36.6	51	37.4	27	57.4	12	24.4	5	50.7
3 to 4 million	49	67.0	35	36.8	20	9.5	11	46.2	5	9.4		

* RBC rise represents the average daily increment in thousands of RBC/mm³. The consistent rise in the average daily increment present in the fourth week seems probably valid according to statistical criteria. Attempts to relate it to iron therapy, change in diet and length of hospital stay failed to show any significant degree of correlation. It also appears to be independent of age and sex.

It is apparent, on comparing the figures for the three groups, that the greater the anemia, the greater the average daily increment of red blood cells. The relation of the erythropoietic response of the body to the degree of anemia is shown even more strikingly in Figure 1. In an effort to determine whether such cases responded in a constant way to an anemia of a given degree regardless of the initial severity of the hemorrhage, the average weekly red blood cell counts for the 1 to 2 million group, beginning with the lowest average count, were plotted on the ordinate axis and the time interval on the abscissa. Having established this curve, the values for the weekly red blood cell counts of the 2 to 3 million group were plotted in such a way that the beginning of the curve (average lowest count) was placed on the curve of the 1 to 2 million group and a similar procedure was followed for the 3 to 4 million group. A graph was thus obtained with a single ordinate axis and multiple abscissal ones.

When this procedure was followed the three curves were found to coincide throughout their significant lengths.

It is, therefore, apparent from this figure that the erythropoietic response of the body is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself. It also appears that though the rate of rise of red blood cells is greater in severe than in mild anemias, nevertheless it takes somewhat longer for patients with a severe initial anemia to attain an essentially normal red blood cell count than for those with a mild one. This is not strictly in accord with the hypothesis advanced

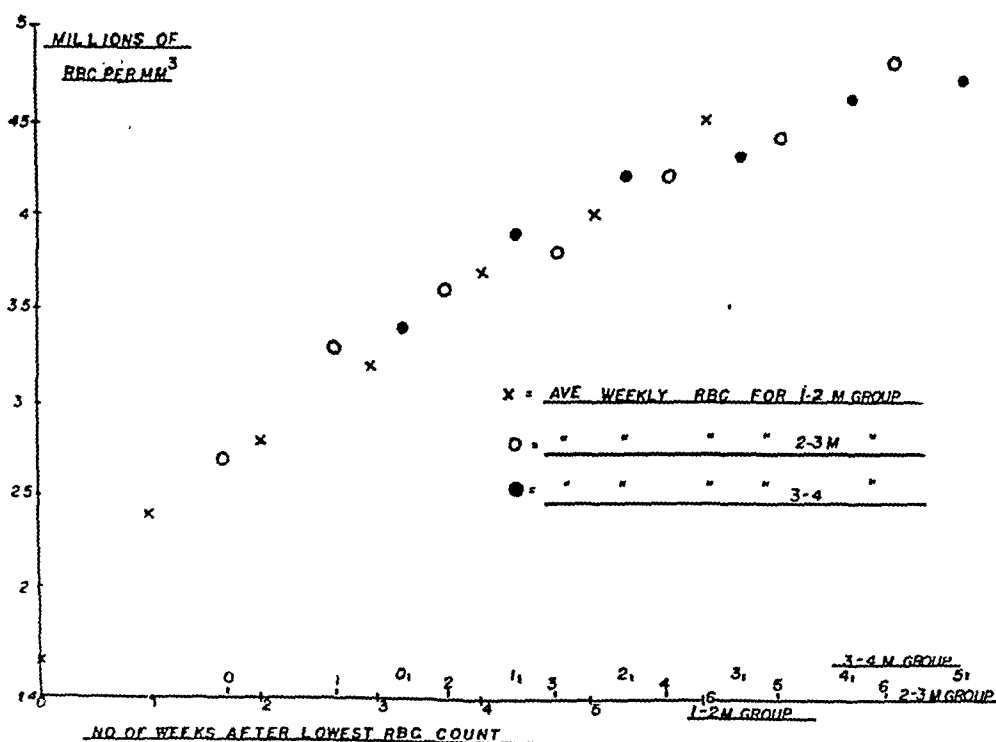


FIG. 1.

by Schjødt,^{15b} that, regardless of the initial degree of the anemia, the red blood cell counts of all cases following hemorrhage "tend to meet in one point, 4.54 million, 33 days after the lowest erythrocyte value was measured." Figure 1 indicates that the cases with the lowest red blood cell counts between 3 and 4 million might in general be expected to attain a normal red blood cell count 3.5 weeks sooner than those in the 1 to 2 million group and 1.5 weeks sooner than those in the 2 to 3 million group.

The rate of erythropoiesis was found to be slightly, but not significantly lower, in the patients over 40 than in the younger group. There was not a sufficiently large number of female cases to permit

a significant correlation of erythropoietic rate with sex though the males seemed to show a tendency to a more rapid rate of regeneration.

In an attempt to evaluate the importance of diet in the erythropoiesis of these cases, both the dietary history before and the dietary treatment after the hemorrhage were considered. Patients whose diets before hemorrhage were the equivalent of, or in a few cases less liberal than, the strict 4th week Sippy regimen showed an average erythropoiesis fully as good as those who had been on a more liberal regimen. It would appear that the 4th week Sippy regimen is as liberal as necessary for satisfactory blood regeneration in the usual case of bleeding ulcer.

Since the majority of these cases were treated by the progressive Sippy regimen, an effort was made to evaluate the relative erythropoietic effect of the first and fourth week diets. This was impossible in the early weeks of treatment because of the small number of cases on fourth week diets during this period and in the later weeks because of the small number of first week diets. In the third week after the lowest count approximately the same number of cases (45 and 58) were treated by each of the two regimens, and the erythropoiesis for that week was essentially the same for the two groups.

This result is not unexpected. It is true that the first week Sippy regimen is a vitamin deficient diet, and if adhered to for a sufficiently long time, might result in anemia. It would hardly be expected, however, that in as short a period as 3 to 4 weeks such a diet could result in retarded erythropoiesis.

Recent reports by Danish investigators^{15a,c} have indicated the superior erythropoietic effect of a liberal "purée diet" throughout the course of treatment of bleeding ulcers over more restricted dietary regimens. Rates of erythropoiesis were available in only 20 cases in the present series treated throughout their hospital stay by a liberal, bland diet without alkali. These cases showed no better erythropoiesis than the group as a whole.

The average daily rise in blood cell count for the entire group (Fig. 1) was compared with the figures reported by Schiødt^{15c} for a group of patients treated by "purée diet" with iron. The values for Schiødt's group were found to be essentially the same as the comparable values in Figure 1.

When the rate of erythropoiesis for the weeks during which cases were given iron therapy by mouth* was compared with the average erythropoietic rate for the group as a whole, no better values were found. In these cases of acute blood loss the administration of iron did not seem to affect the rate of erythropoiesis. It should be emphasized again that no studies were made on the rate of hemoglobin regeneration.

A total of 24 cases received one or more blood transfusions while in the hospital. The erythropoiesis of 17 of these was studied. It

* Usually 2 to 3 gm. of ferric ammonium citrate daily.

was found that the rise in red blood cell counts during the first week after transfusion was on the average 300,000 RBC greater than the corresponding values in Figure 1 in the 1 to 2 and 2 to 3 million groups. After this initial rise the hematopoiesis proceeded at the usual rate depending on the degree of anemia present at that time; the transfusion appeared to exert neither a stimulating nor a depressing effect on the bone marrow. From this it would appear that, when a purely elective transfusion is to be considered for the purpose of speeding recovery, the best effect will be obtained if it is given after the red blood cell count has reached a level of about 3.5 million. Under such circumstances Figure 1 indicates that a transfusion of 500 cc. of whole blood should enable an average patient to attain a normal red blood cell count nearly a week earlier than otherwise. The same transfusion in the presence of a more severe anemia would produce far less proportionate effect due to the higher rate of erythropoiesis at that time (see Fig. 1).

Prognosis. Previous studies in the literature have been directed usually at the mortality rate and immediate treatment of the acute emergency rather than at the subsequent course of the patients who survive the bleeding episode. The essential criterion of recovery from such an episode is the restoration of a normal blood level. Figure 1 enables one to estimate the length of time necessary for this process in the average case as reckoned from the lowest red blood cell count. It is of interest to note that in 44% of the surviving patients the lowest red blood cell count was on entry and that it occurred within 1 week after entry in another 34%. Only 13 patients failed to reach their lowest red blood cell count within 2 weeks after entry, and of these only 3 had lowest red blood cell counts below 2 million. The other patients who failed to reach their lowest red blood cell count for an equally long period of time and who also showed occult blood in the stools, did not reach such a critical anemia despite their long continued bleeding.

Once the patient has reached his lowest red blood cell count his recovery time appears to depend on the degree of the anemia as noted above. On the average, if the lowest red blood cell count is between 1 and 2 million it should require a little over 6 weeks to attain a red blood cell count of 4.5 million. If the lowest red blood cell count is between 2 and 3 million, it should require above 5 weeks, and if it is between 3 and 4 million, about 3 weeks. Should the rate of recovery in an individual case lag much behind the average, some complication might well be suspected.

Mortality. The efficacy of the treatment of the acute episode of bleeding usually is assessed in terms of mortality. In the present series 20 patients died. In 10 of these hemorrhage was considered to be the principal cause of death, and it contributed directly to the death in 3 others, a net mortality of 5.5%. In the 7 remaining cases the hemorrhage was not directly contributory to death; 1 died of

cerebral hemorrhage after the red blood cell count had returned to normal, 1 died of a transfusion with incompatible blood and 1 of dehydration, uremia and pneumonia without appreciable anemia. There were 5 postoperative deaths, but only 1 of these had a severe preoperative anemia (1.7 million); the other 4 did not (3 to 5 million). Only 4 cases died within 48 hours after the presumed onset of the hemorrhage, 3 died within the first week after the onset and the remainder at longer intervals. Of the 13 cases in which anemia contributed significantly to death, the median age was between 60 to 65 years and the youngest was 54 years as compared with a median age of 45 years for the entire series, which is essentially in accord with the figures for other series.^{3,5,7b,11} It appears that young individuals with bleeding ulcers rarely die, and when they do, it is usually as a result of complications, rather than exsanguination. It also seems that in this series death from exsanguination was not, as a rule, sudden even in old people but occurred only after several days of continued bleeding. The literature varies on this point.^{8a,13a}

It appears that judged by the criterion of mortality also, the Sippy regimen is a satisfactory method of treatment for bleeding peptic ulcer. Though lower mortality rates have been reported,^{6,9,13a,b,14} the figure of 5.5% compares favorably with the mortality in most similar series.^{1,2,5,12,17}

TABLE 2.—MORTALITY IN BLEEDING PEPTIC ULCER.

Name.	No. of cases.	Mortality rate (%).
Aitken	255	11.0
Bulmer	467	9.9
Goldman	349	11.1
Gram	106	2.0
Hurst and Ryle	82*	4.8
	258†	1.6
Lahey	346	5.0
Meulengracht	368	1.3
Umber	433	9.5

* Guy's Hospital cases.

† Private practice.

Each of the series in Table 2 consists of patients with gross hematemesis or melena. However, the percentage of proven ulcer in any of the groups in which it could be determined was far below 86%, the figure for the present series. The extent and the direction to which the inclusion of cases of hematemesis or melena not resulting from peptic ulcer has influenced the mortality statistics in these series seems difficult to determine.

Contrary to statements^{2,3,11} that the mortality in males is appreciably greater than in females, there appears no significant difference between the sexes in this series; 2 of 46 females and 11 of 184 males died as a result of hemorrhage.

Opinion has differed also regarding the prognosis of bleeding ulcer in patients with a history of previous hemorrhage. In this series the mortality in patients with previous hemorrhage does not differ significantly from that for the group as a whole.

Summary. 1. Records of 237 cases of bleeding peptic ulcer have been analyzed with special reference to symptomatology, the anemia produced by the hemorrhage and the subsequent course of the patient.

2. Over one-third of the patients noted symptoms of weakness, syncope or dyspnea before any external evidence of bleeding. Evidence of exacerbation of the activity of the ulcer prior to the bleeding was found in only 28% of the cases.

3. Approximately one-fourth of the patients in each decade had had ulcer symptoms for less than 1 year and over 8 years respectively before the hemorrhage.

4. Severity of hemorrhage appeared quite independent of the age and sex of the individual.

5. Age appeared to have no relation to the number of previous hemorrhages.

6. The weekly rate of erythropoiesis was determined for 177 cases on the basis of the lowest red blood cell count. The rate of erythropoiesis appeared strictly dependent on the degree of anemia present at the time, regardless of the duration of the illness and the initial severity of the anemia.

7. The observed erythropoietic rate for cases in this series, the large majority of which were treated on a Sippy regimen, was fully as good as that reported for patients treated with a liberal, "puréed diet" and iron.

8. Beyond the actual increment of donated cells transfusion appears to have no effect on the rate of erythropoiesis.

9. A net mortality of 5.5% was present for the series. This appeared to be independent of sex or number of previous hemorrhages.

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CYSTEINE HYDROCHLORIDE AS AN ANTICOAGULANT FOR CLINICAL USE.*

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The Conditions Produced by Increased Coagulability of the Blood. Much study has been devoted to the hemorrhagic diseases, but the disorders resulting from an excessive tendency of the blood to coagulate have received little attention. Such conditions unquestionably exist. Thrombosis of blood in normal vessels has been demonstrated experimentally by Flexner,⁴ Mills,¹³ and others, following injection of foreign protein and organ extracts, by Kusama⁹ following injection of a variety of substances, by Stuber and Lang²³ following exposure to carbon dioxide, by Meyer¹² following exposure to carbon monoxide, and by many other investigators using other means. Common examples of clinical states in which thrombosis occurs in apparently normal vessels are the thrombophlebitis occurring in pregnancy, and after surgical operations, "spontaneous" thrombosis of the retinal vein in young subjects, thrombophilia,¹⁷ and polycythemia. Evidence has recently been adduced^{19a} which suggests that multiple sclerosis and certain forms of "encephalitis" (for example, the postinfectious type) are the result of thrombosis of small cerebral vessels, and it was this aspect of the problem which called it to our attention. There are doubtless other diseases which could be added to the list.

The conception of thrombosis in *normal* vessels as a result of a disorder of the blood plasma has not been easily accepted. Prior to Virchow's time, injury to the vessel wall was generally held to be an essential first step in thrombosis. Modern pathologists recognize that clotting may occur in normal vessels. Aschoff¹ for example, says: "... Thrombosis is the function of a number of variables. . . . Among these may be mentioned here, first, changes in the blood plasma (diminished or increased coagulability), secondly, changes in the blood elements (increased or decreased powers of agglutination), thirdly, changes in the blood flow (slowing and formation of eddies), and lastly, changes in the vessel wall itself (endothelial damage). An enquiry into the mechanism of thrombosis

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shows that sometimes one factor, sometimes another plays the principal rôle The existence of increased coagulability, and the likelihood that it is a promoting factor, or better, an accompanying phenomenon, cannot be denied. . . . We do not know as yet anything of the phenomena which precede agglutination of platelets, and which are the very earliest factors in thrombosis I can find in the literature no well-authenticated cases in which thrombosis has really been brought about by changes in the endothelium, a factor which is regarded by many authors as of special importance."

Since the above statement was written, a good start has been made toward learning more about the stability of the plasma under various circumstances.¹⁰

Previous Attempts to Decrease the Coagulability of Circulating Blood. A number of substances have been used to prevent coagulation of circulating blood in animal experiments. Outstanding among these are hirudin⁵ and heparin.⁸ Pickering and Hemingway¹⁸ succeeded in preventing thrombosis even at the point of contact with a foreign body by administration of heparin. Peroral administration of citric acid was reported by Brooks and Crowell² to reduce artificially produced thrombi. Marris¹¹ saw arrest of thrombosis in patients after repeated intravenous injection of sodium citrate, but others³ have employed citrates to promote coagulation. Sodium thiosulphate has been recommended for the treatment of thrombophlebitis and thrombangiitis obliterans,²¹ but evidence of its effectiveness is not clear. More recently, Murray and Best¹⁶ and others⁶ have suggested the use of a more potent heparin by intravenous drip. The effect of the heparin may apparently be made as powerful as is desired, as Murray and Best have shown (loc. cit.), but it lasts only 4 hours after a single dose. Long continued use might become dangerous because repetition of an injection before the effect of the first dose has worn off might cause serious or even fatal bleeding. Therefore, heparin may be of use in the prevention of postoperative thrombosis, but it could not be employed over long periods of time in the conditions characterized by a chronic lability of the plasma. As it was exactly such conditions for which a treatment was sought, a search was instituted for an anticoagulant effective when given by mouth.

Previous Observations on the Anticoagulant Activity of Cysteine Hydrochloride. In a search for some substance which might be used clinically as an anticoagulant over long periods of time, our attention was attracted by the paper by Sterner and Medes²² on cysteine hydrochloride. The anticoagulant effect of this substance was first observed, entirely by chance, by Mueller and Sturgis in 1932.¹⁵ They were using it as one of a series of growth-promoting sulphur-containing substances, and noticed that it inhibited the clotting of plasma used as a medium. Sterner and Medes studied its action in more detail, and found that it acted as an antiprothrom-

bin. They state that it prolongs both the bleeding time and the clotting time, whether injected intravenously or administered by mouth. The graph which is presented shows a prolongation of bleeding time from 4 to 6 minutes, but does not demonstrate a prolongation of clotting time, using "the 8 mm. tube method." In *in vitro* experiments, a marked prolongation of clotting time (from less than 10 minutes to 50 minutes) occurred with molar concentrations of 0.16 to 0.64 of cysteine. Methionine, taurine, and taurocholic acid exhibited somewhat similar properties.

In recent experiments on the production of "encephalitic" lesions by intravenous injection of coagulants, we found that cysteine hydrochloride given intravenously or by mouth would prevent death from several times the usual lethal dose of a well-standardized lung extract.⁷ It was an obvious step, therefore, to test its effects further in animals and in human beings.

Methods. The following technique for determination of blood coagulation was finally worked out as the most dependable one, after a number of other methods had been tried and discarded: a series of 15 test tubes 8 by 75 mm. was set up in a wire rack and approximately 1 cc. of blood was put into each. The technique was rigidly standardized. Special care was taken to clean the syringes and test tubes in a uniform fashion, and only new 18-gauge needles were employed. Any determinations in which there was a delay in securing blood were discarded, as were those in which bubbles appeared in the syringe or tube. Blood was taken by cardiac puncture in unanesthetized dogs, and from the arm-veins of patients who were specially chosen as permitting sure and easy venipuncture. The determinations were carried out in rooms maintained at a temperature between 25° and 30° C. At certain intervals, usually of 10 to 20 minutes at the beginning, closer toward the end of the observation, one tube was inverted and its content poured out. The time at which the first signs of a clot were observed and also that at which the entire content of one tube was clotted, so that no liquid blood could be poured out even by jerking the tube, were recorded. In a series of experiments the times were charted for the appearance of the first clot, and those at which approximately one-half, three-quarters and the whole amount of blood were clotted. (Figure 3 shows one of these observations carried out over 10 days with 7 determinations during this period.) Each of the 15 specimens is handled only once. A liquid residual of blood poured into another tube usually clots within a few minutes, while untouched specimens will remain partly liquid for a considerable length of time. Care was taken to discard specimens in which sedimentation had occurred. Sanguinolent serum after complete coagulation was easily distinguished from unclotted blood. Whenever one specimen was found completely clotted the following tube was examined until either all were found clotted or as occurred in some instances, one specimen was not quite clotted. In these cases, the observation was continued. No experiment was accepted until three consistent determinations had been secured before administration of the drug.

It is fully realized that the determination described above differs essentially from the one used routinely for the clinical observation of clotting time. This is defined for instance in the Thorndike Laboratory¹⁴ as the time after which a surface clot has formed thick enough

to hold the amount of 2 cc. of blood in a tube of certain dimensions when the tube is inverted. When this method is used the normal clotting time is 12 minutes for specimens kept at 37° C. in a thermostat. This might correspond to the "first clot" stage in our determination (Fig. 1a).

The reason for abandoning this or some similar arbitrary endpoint was the following: In tubes of the size used in our experiments, the first clot is as often as not a layer adherent to the glass. This slowly becomes thicker and at some later time usually the surface layer coagulates. It is then still possible by shaking the tube to

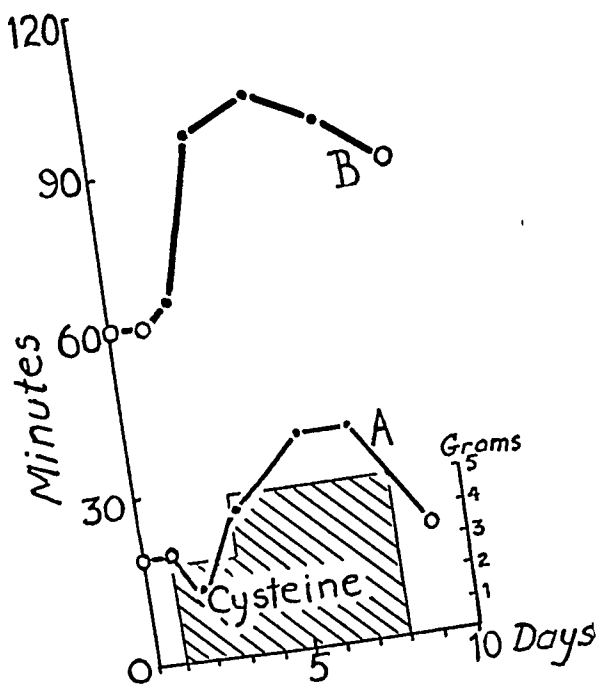


FIG. 1.—Prolongation of coagulation time of Patient H. during 8 days of treatment with cysteine hydrochloride by mouth. Curve A, first clot. Curve B, completely clotted. Note persistence of effect for a day after discontinuance of the drug.

obtain blood which is still liquid but will clot promptly in another tube. The determination of the time for complete coagulation appeared to be more consistent than that required for the appearance of the first signs of clot. It is marked by the moment when retraction begins and serum is squeezed out. Figures were consistently obtained which were much higher than those usually given. Thus, coagulation times up to 60 minutes in normal dogs and up to 105 minutes in man during a control period were observed, after the technique had been thoroughly systematized. The fact that observations were made at room temperature instead of at body temper-

ature accounts for part of the difference. It was also observed²⁰ that blood taken with a needle of a large gauge remains liquid much longer than blood taken with a small gauge needle.

Animal Experiments. Satisfactory experiments were carried out in 8 dogs. The dogs were trained to lie still for a cardiac puncture.

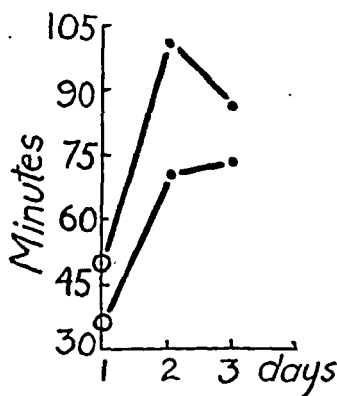


FIG. 2.—Coagulation times (in minutes) of 2 dogs, each of which received 5 gm. cysteine hydrochloride by stomach tube immediately after the first sample of blood was taken.

The cysteine was injected intracardially in doses of 0.2 gm. per kilo in 4 experiments. There was a subsequent rise of 40 to 100% in 3 of them, which reached its height in a few hours, and was still apparent 24 to 40 hours after injection. A typical curve is shown in Figure 3. Cysteine hydrochloride was given by stomach-tube in

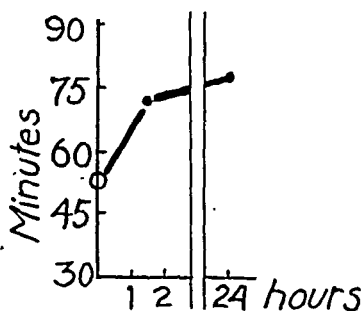


FIG. 3.—Coagulation times (in minutes) of a dog which was given 3 gm. cysteine hydrochloride intracardially immediately after the first sample of blood was taken.

8 other experiments, in doses of 0.4 to 0.75 gm. per kilo. Four of these experiments had to be discarded because of errors in technique; but in the remainder an increase of clotting time of 25 to 100% was obtained, which in several instances lasted for 48 hours after the injection (Fig. 2).

Observations on Patients. All of the patients studied suffered from multiple sclerosis. They were chosen both as having the disease in a relapsing form, and as satisfactory subjects for venipuncture.

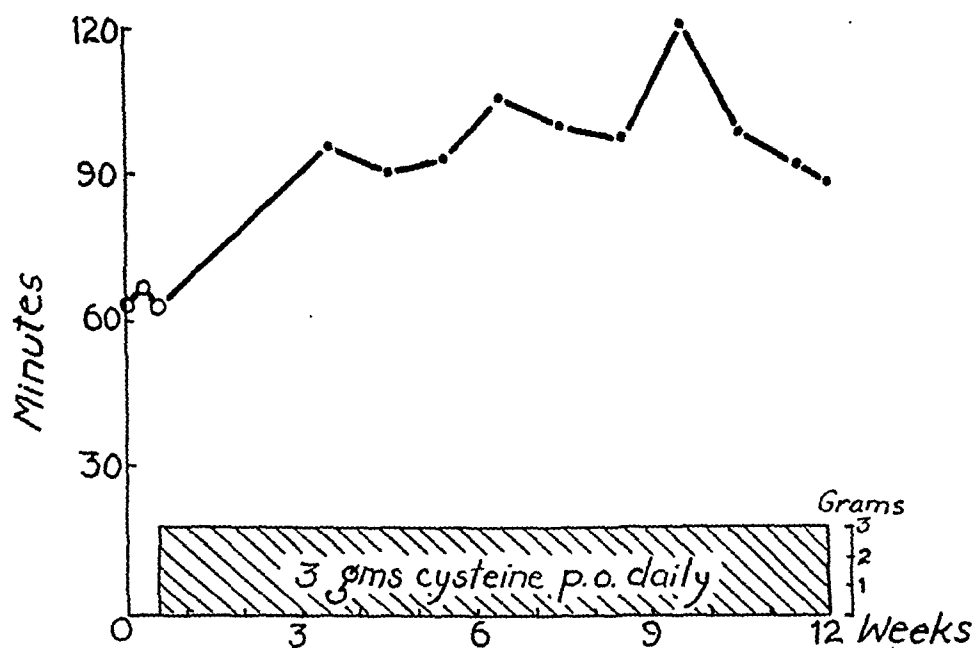


FIG. 4.—Alterations in the clotting time of Patient W.D.N. over a period of 12 weeks on cysteine hydrochloride by mouth.

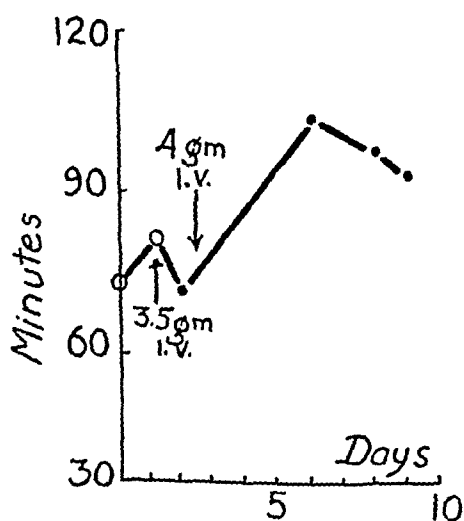


FIG. 5.—Alterations in coagulation time produced by 2 intravenous injections of cysteine hydrochloride in saline, 4 days apart (Patient M.).

After three or more control observations a day or two apart, administration of cysteine was begun. In 6 instances, cysteine was administered intravenously in 10% solution in normal saline. In 17 other cases, it was given by mouth, in large capsules, at a dosage of 3 to

5 gm. daily. When given in larger doses, gastric distress and malodorous eructations often occurred. One patient developed an extensive area of ecchymosis on her right calf with some ecchymotic spots on her left leg as well. This occurred after 11 days of intensive treatment. Platelets had been reported normal previous to the administration of the drug and since there was no history of bruising easily, it was assumed that this was probably due to the action of cysteine. A repeated platelet count showed 400,000 platelets per c.mm. and a bleeding time of $3\frac{1}{2}$ minutes. Two patients complained of an increased menstrual flow, which recurred each month during the course of treatment. The drug was otherwise well borne.

In 17 out of these 23 instances, an increase in coagulation time was observed. The rise varied from 30 to 90%. Typical records are seen in Figures 1, 4 and 5. In several instances, there was a delay of 1 or 2 days before the increase occurred.

The patients mentioned are not the only ones who have taken large amounts of cysteine. Seven other patients suffering from multiple sclerosis have taken similar doses by mouth daily for periods varying from 6 months to over 2 years, with no untoward symptoms. In this group, studies of coagulation could not be carried out.

Therapeutic Results. The period of observation is too brief and the series too small to permit evaluation of therapeutic results. Obviously, treatment with an anticoagulant should not be expected to improve the symptoms of multiple sclerosis,^{19b} nor are relapses entirely prevented by the amount of the drug which can be given. Pending the development of more powerful and dependable anticoagulants of prolonged action, however, it seems worth while to continue the observations.

Other Possible Indications for Treatment With Cysteine. There may be a question whether cysteine is a sufficiently active anticoagulant to prevent postoperative thrombosis. It appears to be harmless in moderate doses, however, and is comparatively inexpensive. It might be even more advantageous in the treatment of established thrombosis, to diminish the likelihood of extension.

There are other conditions in which an anticoagulant which is effective when given by mouth might be useful, for example, cerebral or coronary thrombosis, phlebitis migrans, and subacute bacterial endocarditis. We have used it in one case of the latter condition, but in such an advanced stage that its failure to modify the process is difficult to evaluate. An extensive thrombosis of the femoral vein complicating lead encephalitis in a child of 18 months was arrested following its use.

Summary. 1. The intracardial injection of cysteine hydrochloride in dogs was followed by a rise in coagulation time of 40 to 100% in 3 out of 5 experiments.

2. The administration of cysteine hydrochloride to dogs by stomach tube was followed by an increase of clotting time of 25 to 100% in all technically satisfactory experiments.

3. Cysteine hydrochloride was also administered by mouth to 23 patients in whom the diagnosis of multiple sclerosis had been made. In 17, a rise of coagulation time was observed, which varied from 30 to 90%.

4. Cysteine hydrochloride is well tolerated by most patients in doses up to 3 gm. per day, over many months. No serious symptoms have been observed to follow its use.

5. It is therefore suggested as an anticogulant of rather low efficiency for use over long periods of time, for conditions in which such an agent might be valuable.

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A STUDY OF THE CLOTTING DEFECT IN HEMOPHILIA: THE DELAYED FORMATION OF THROMBIN.*

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No very general agreement exists concerning the nature of the clotting defect in hemophilia. The literature of this subject has been reviewed by Wöhlisch,¹¹ and more recently in the papers of Patek and his associates.^{7,8} Practically all workers agree that the plasma fibrinogen is essentially normal in amount and reactivity, and that no excess of antithrombin is present. Our results substantiate these views. It follows, by exclusion, that the defect lies

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in one or more of the factors concerned in the formation of thrombin. However, no quantitative studies have been made on the speed with which prothrombin is converted into thrombin in hemophilic blood. To follow this reaction we have developed an accurate method for the measurement of the prothrombin conversion rate. Using the prothrombin titration technique devised in this laboratory,^{9,10a} the residual prothrombin content of the plasma (or serum) is determined at intervals, beginning shortly after the blood is drawn and continuing until the prothrombin supply is practically exhausted a number of hours later.

The experiments which follow show that in hemophilia the prothrombin conversion rate is extremely slow throughout the entire period of observation. It is also shown that the conversion rate is brought to normal by adding an extremely minute amount of a thromboplastic organ extract. If given time, the formed elements of the hemophilic blood also liberate materials sufficient to accomplish the same result.

Experimental Observations. Five cases of hemophilia were studied. Most of the data presented were from 1 patient who was available for continuous study over a period of about 7 months, but practically all of the experiments were repeated on one or more of the other patients.

In all 5 cases the prothrombin content of the plasma, determined by the method of Warner, Brinkhous and Smith,^{9,10a} was within the limits of normal. The highest value was 110% of the normal control, the lowest value 90%. The fibrinogen content of the plasmas, determined by the method of Jones and Smith,⁵ was within the normal range of 340 to 400 mg. per 100 cc.

Tests for antithrombic activity also gave normal values. Both plasma and serum, incubated with thrombin solutions, destroyed thrombin in the same amounts and at the same rates as did the normal controls. Also, thrombin solutions clotted hemophilic plasma with the same rapidity as they clotted normal plasma. This confirms previous observations of other workers and serves to show that the fibrinogen of hemophilic plasma is normally reactive.

The Slow Conversion of Prothrombin Into Thrombin in Hemophilia. Chart 1 shows the very slow rate at which prothrombin is converted into thrombin in hemophilic blood. In this experiment, the hemophilic blood was first allowed to stand for 15 minutes at 28° C. to permit, as nearly as possible, a standard amount of disintegration of platelets and blood cells. Cell-free plasma was then obtained by centrifugalization (4000 r.p.m. for 15 minutes). At this time the prothrombin content of the plasma was still essentially the same as that of the oxalated control plasma from the same individual, showing that in 30 minutes no detectable amount of prothrombin had been converted. This is in accord with the fact

that the plasma did not clot until another 60 minutes had elapsed. Following clotting, the prothrombin titer fell extremely slowly. After standing 24 hours, 50% of the prothrombin still remained unconverted, and to convert 90% of the prothrombin a total period of 3 days was required.

The normal control blood in this experiment was treated in the same manner as given above. It clotted, however, in 10 minutes, so that on centrifugalization, serum was obtained instead of plasma.

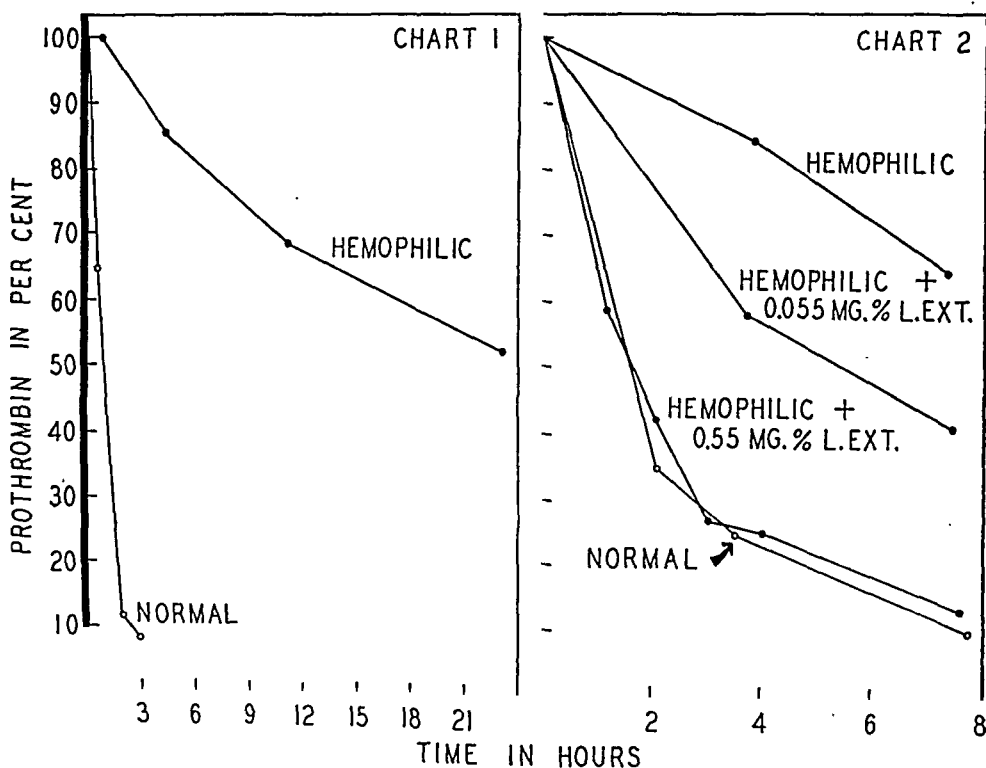


CHART 1.—The blood in each case was allowed to stand for 15 minutes. It was then centrifugalized for 15 minutes at 4000 r.p.m. The residual prothrombin content of the serum (or plasma), determined at intervals, is expressed in per cent, using its oxalated control plasma as 100%. The blood was kept at 28° C. throughout the course of the experiment.

CHART 2.—Each blood sample was centrifugalized immediately, after which the residual prothrombin content of the serum (or plasma) was determined at intervals.

The serum, analyzed immediately, had already lost 35% of its prothrombin within this 30-minute period, and within 3 hours over 90% of the prothrombin had been converted.

By comparing the prothrombin conversion rates at a given level of prothrombin, it is evident that the amount converted in unit time is fully 30 times as great in the normal as in the hemophilic serum. This slow formation of thrombin in hemophilia allows the thrombin to be destroyed by antithrombin almost as rapidly as it is

formed. At no time did the serum contain more than the merest trace of thrombin, and on adding fibrinogen many minutes would elapse before a clot would form. In normal serum, on the other hand, the thrombin titer is such that a clot typically forms in 10 to 60 seconds.

Associated with the low thrombin titer in hemophilic blood is the great length of time required for the complete clotting of its fibrinogen. After the onset of clotting, successive crops of fibrin appear over a period of 1 to 2 hours or even longer. In contrast to this slow clotting, only a very few minutes are required for the complete conversion of fibrinogen into fibrin in normal blood.

The Effect of Thromboplastin Upon the Prothrombin Conversion Rate in Hemophilia. It is known that organ extracts, rich in thromboplastin, accelerate the clotting of hemophilic blood. We have undertaken to test in a quantitative way the effect of such extracts upon the prothrombin conversion rate. The experiments which follow show that the conversion rate in hemophilia can be brought within the normal range by adding to 100 cc. hemophilic blood less than 1 mg. of the material extracted from lung.

One hundred grams of ground beef lung were extracted for 48 hours at 5° with 100 cc. saline (0.9% NaCl). The extract, obtained by centrifugalization, was neutralized (pH 7.4). It contained 3.3 gm. % total organic solids. One portion of the extract was diluted 1000 times with saline; another portion 10,000 times. To 0.2 cc. of each was added 1 cc. freshly drawn hemophilic blood. The first tube, containing 0.55 mg. % extracted material, clotted in 9 minutes; the second, containing 0.055 mg. % extracted material, clotted in 21 minutes. One control tube was prepared by mixing 0.2 cc. saline with 1 cc. hemophilic blood; another by mixing 0.2 cc. saline with 1 cc. normal blood. The hemophilic clotted in 55 minutes; the normal in 10 minutes.

Four mixtures, duplicates of the 4 above, were then prepared and centrifugalized immediately (4000 r.p.m. for 15 minutes at 5°). The plasma (or serum) was then removed and allowed to stand 8 hours at 28°. The residual prothrombin content of each mixture was determined at intervals during this period. The prothrombin conversion curves are given in Chart 2.

In this experiment an effort was made to reduce the breakdown of cells and platelets by immediate centrifugalization of the blood samples at a low temperature. This had little effect on the hemophilic specimen, for the prothrombin conversion rate (Chart 2) was approximately the same as that shown in Chart 1. In the normal blood these precautions were rather effective, however, for the prothrombin conversion rate was less rapid than in the previous experiment. The disintegration of blood cells and platelets which occurred here probably did not exceed that of the normal blood during its 10-minute clotting period. Nevertheless, the conversion was still relatively rapid: at comparable levels of prothrombin it was almost 10 times as rapid as in the hemophilic blood.

The effect of adding small amounts of lung extract is also shown

in Chart 2. It will be noted that addition of less than 1 mg. extracted material per 100 cc. hemophilic blood is sufficient to restore the prothrombin conversion rate to normal. Addition of less than 0.1 mg. per 100 cc. has a definite, but less pronounced, effect.

The striking effect of such minute amounts of lung extract is all the more remarkable when one reflects that the product is a crude mixture containing much inert material. It is a reasonable assumption that the active principle in the extract is thromboplastin, for it is known that saline extracts of lung have great thromboplastic power. One cannot exclude the possibility that they may also supply important clotting factors other than thromboplastin, but there is as yet no evidence that this is so.

The effect of adding large amounts of lung extract was studied also. Under these circumstances the prothrombin is converted very rapidly into thrombin, and the prothrombin conversion rates, both normal and hemophilic, are identical. If the undiluted lung extract is added to an equal volume of normal and of hemophilic plasma, 85 to 90% of the prothrombin is converted in 50 to 55 seconds after recalcification in each case.

A similar result is obtained when one treats diluted plasma with an excess of thromboplastin. In the titration of prothrombin, the plasma is diluted routinely to a prothrombin concentration of 1 unit. In the presence of lung extract and calcium, there is complete conversion of the prothrombin in hemophilic plasma in 4 minutes, exactly as in the normal control plasma.

It has been suggested^{1,2} that the prothrombin in hemophilia is relatively unreactive and hence is responsible for the clotting defect. With the methods used in the experiments just cited, we have already shown that the prothrombin of human plasma is less reactive than that of many other species.^{10b} This slow convertibility in man is a handicap in the control of hemorrhage, but the present experiments would indicate that in hemophilia this handicap is no greater than it is normally.

The Formed Elements of the Blood in Hemophilia: Their Effect on the Prothrombin Conversion Rate. That hemophilic platelets contain a thrombin-forming factor, analogous to that of our lung extract, has been shown by many workers. The experiments of Opitz and Zweig⁶ are especially significant. They allowed citrated hemophilic blood to stand in contact with its cells and platelets. When recalcified 12 to 24 hours later, clotting occurred in a normal time. Platelet-free plasma, however, was not improved by standing. We have confirmed these findings, and have extended our observations to place this experiment on a quantitative basis.

The prothrombin conversion rates were determined in blood and in plasma which had been allowed to stand for 24 hours in citrate (Chart 3). The prothrombin conversion rate of the aged cell-free plasma was not affected by the incubation. It was practically

identical with the fresh hemophilic control, not shown in the chart. On the other hand, hemophilic plasma incubated in contact with the cells acquired the ability to form thrombin at practically the same speed as does normal plasma. This shows definitely that the cellular elements are concerned, and that, if given time, they liberate the thrombin-forming factor in amounts adequate for a normal rate of prothrombin conversion.

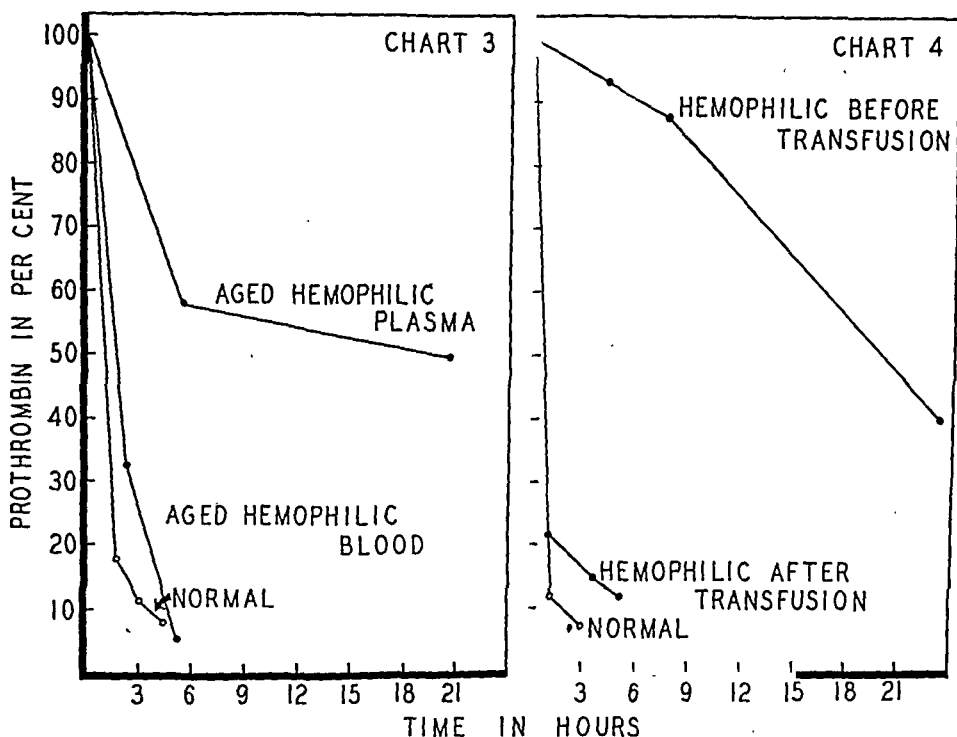


CHART 3.—Each blood sample was mixed with one-tenth its volume of 2.85% sodium citrate. The normal control plasma was recalcified immediately after centrifugalization. Its clotting time was 7 minutes. The residual prothrombin content of its serum was then determined at intervals. Hemophilic plasma, obtained at the same time, was allowed to stand 24 hours at 28° C. before recalcification. It clotted in 68 minutes. Its residual prothrombin was then determined at intervals (upper curve). The whole citrated hemophilic blood was allowed to stand 24 hours at 28° C. before centrifugalization. The plasma obtained at that time was immediately recalcified. Its clotting time was 10 minutes. The residual prothrombin content of the serum was determined at intervals (middle curve).

CHART 4.—The blood samples were treated as in Chart 1.

One theory of the clotting defect in hemophilia centers about defective platelet function. The evidence available indicates that the platelets contain a normal amount of thromboplastin, although it must be admitted that methods for assay of thromboplastin are highly inadequate. Morphologic studies of the platelets, on the

other hand, show that they are unduly stable.⁴ This would indicate that their thromboplastin, although normal in amount, is liberated more slowly than in normal blood. In harmony with this view are our observations that approximately 24 hours are required for the release of sufficient thromboplastin to give normal clotting. It is significant that when normal blood is collected carefully to prevent undue destruction of cells and platelets, the prothrombin conversion is greatly lengthened (see Charts 1 and 2). This suggests that if normal blood were collected entirely free of formed elements and their distintegration products by the method of Fuchs,³ it might be quite similar, if not identical, to the plasma of hemophilic patients. With such plasma as a control it might be possible to make a crucial test of the theories that the prothrombin is relatively unreactive or that its conversion is blocked by some inhibitor.

The Effect of Transfusion in Hemophilia. Blood transfusions remain one of the most successful means of controlling hemorrhage in hemophilia as well as of preparing these patients for operation. After transfusion, the clotting time often becomes normal and may remain so for many hours. We have had the opportunity of observing the effect of transfusion in several cases. One of these was given 300 cc. of normal blood in preparation for tooth extraction. Prior to transfusion the clotting time was 100 minutes; 12 hours afterwards it was 10 minutes. The prothrombin conversion rate, given in Chart 4, was quite slow before transfusion, but when tested 12 hours afterwards it was found to be normal.

One can postulate that normal plasma supplies some factor which hemophilic plasma lacks, but it is even more likely, in our opinion, that the cells and platelets of the donor's blood supply the missing element. A simple explanation is that the element so supplied is thromboplastin. This possibility needs further study, both because of its theoretical importance, and because of the therapeutic implications.

Summary. A quantitative study of changes in the prothrombin titer of hemophilic blood shows that its prothrombin is converted very slowly into thrombin. This delayed prothrombin conversion can be corrected by adding less than 1 mg. of crude thromboplastin to 100 cc. hemophilic blood. Evidence indicates that the prothrombin and fibrinogen are normal in amount and in reactivity in this disease. There is no excess of the antithrombin. Emphasis is placed upon the formed elements of the blood and the sluggishness with which they liberate thromboplastin.

The beneficial effects of transfusion in hemophilia were studied.

The writer is indebted to several members of the Departments of Pediatrics and of Internal Medicine, especially to Drs. R. L. Jackson, E. L. DeGowin, and O. D. Thatcher, for their generous cooperation throughout the course of this study.

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BLOOD STUDIES IN LYMPHOGRANULOMA VENEREUM; WITH SPECIAL REFERENCE TO SERUM PROTEINS,

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In the past decade the literature on various aspects of lymphogranuloma venereum has been accumulating rapidly. In the United States the first paper on the subject appeared in 1932.² However, in spite of the many phases of the disease which have been described and discussed, only two groups of authors have written concerning the derangement of serum proteins which usually occurs.

Williams and Gutman,¹² in 1936, were the first to call attention to the hyperproteinemia (hyperglobulinemia) which may occur in this disease. An increase in serum proteins was found in 10 of the 12 cases studied, and in 9 the globulin was sufficiently increased to cause a reversal of the albumin-globulin ratio. The urine of none of these patients contained Bence-Jones protein. Subsequently Williams and Gutman⁵ reported total serum protein values of over 8 gm. % in 26 of 35 patients with lymphogranuloma venereum. In all cases the hyperproteinemia was due to high serum globulin values. In a third paper, Gutman and Williams³ noted that the Wassermann reaction was anti-complementary in 22% of patients who gave positive Frei tests. In addition, Gutman and Wise⁴ described their results with the formal-gel reaction in relation to the hyperproteinemia of lymphogranuloma venereum as well as in that due to other conditions. A positive test occurred in the majority of cases, if the preparation was allowed to stand for at least several hours, or as long as 24 hours.

In 1937, Rosen, Rosenfeld and Krasnow¹⁰ published a preliminary study of the serum lipids and proteins in lymphogranuloma venereum. They found the lipids definitely lowered. Globulin was always high although the total serum proteins were not always elevated. These authors noted a significant relationship between the duration of the disease and alterations in the protein content of the serum; the longer the duration of the disease, the greater the alteration in the serum proteins.

In this paper, we are reporting the serum protein values in 67 cases of lymphogranuloma venereum. In addition to the serum protein determinations the sedimentation rate, Costa reaction, aldehyde test and "serum and water test" were carried out in many cases. Either the Wassermann or Kahn test, or both, were done in all but one case. Red blood cell counts, hemoglobin and hematocrit determinations were done in over half the cases.

Material. The clinical material consisted of a group of 43 patients from the Vanderbilt University Hospital (V. U. H.), and a group of 24 patients followed at the Nashville General Hospital (N. G. H.) (Tables 1 and 2). Many of the V. U. H. patients had been under observation for years, either as the result of the lymphogranuloma infection, or for other reasons. The cases were accepted for this study consecutively as they appeared in the clinic. No cases in which a definite diagnosis of lymphogranuloma venereum was made were discarded.

The diagnosis of lymphogranuloma venereum was considered established if a clinical picture compatible with either the more acute phases of the infection, or its complications were present and if a positive reaction was obtained with one or more Frei antigens. Frei tests were generally done with more than one antigen. The antigens employed were commercial mouse-brain antigens, and human antigens made by us from bubo-pus or gland emulsions. Some patients were tested with as many as four different antigens for comparative purposes.

The subjects with rectal lesions have been separated into groups according to the nature of the lesions as follows: 1, acute proctitis, those cases which were in the early stages of acute ano-rectal ulceration, and in which no scar tissue had as yet developed; 2, chronic proctitis, those cases of ano-rectal ulceration which had progressed or terminated in extensive scar tissue formation. The cases of chronic proctitis in turn have been further subdivided into (a) active, and (b) inactive. The term *active* has been applied to those cases of chronic proctitis in which acute or subacute inflammatory reaction exists. This does not *imply* that the inflammatory reaction is caused by the virus of lymphogranuloma venereum. *Inactive* cases of chronic proctitis are those in which no inflammatory reaction is present. We have classified the strictures appearing in the chronic group under the following descriptive headings: diaphragmatic, tubular and funnel.

The duration of symptoms as given in the tables refers to the time elapsed from the onset of symptoms until the date of the first serum protein determination. Other laboratory studies were done within a few days at most of the first protein study.

Method. Serum proteins were determined by the colorimetric method of Minot and Keller⁷ which gives values similar to those obtained by the Kjeldahl method. At V. U. H. the accuracy of this method is checked at intervals by parallel determinations by the micro-Kjeldahl technique, and in this study some of the grossly abnormal values were checked in the same way.

TABLE 1.—DATA ON FEMALE PATIENTS WITH LYMPHOGRANULOMA VENEREUM STUDIED AT VANDERBILT UNIVERSITY HOSPITAL.

Number	Race.	Age.	Diagnosis.	Activity.	Duration of disease.	Date of blood study determinations.	Total serum protein.	Serum albumin.	Serum globulin.	A/G ratio.	Sedimentation rate.	Costa.	Aldehyde.	Serum and water.	Hemoglobin.	Red blood cells.	Hematocrit.	No. of positive Frei tests.	Wassermann and Kahn.
1	C	47	Rectal stric.	Chr. act.	20 yrs.	12/20/37	10.60	3.76	6.84	0.55	22	x	?	?	12.5	3.8	38	3	K—
2	C	37	Rectal stric.	Chr. act.	12 yrs.	3/26/38	11.76	3.68	8.08	0.45	24	x	?	1+			32	1	W—
3	C	37	Rectal stric.	Chr. act.	11 yrs.	12/20/37	10.60	2.91	7.69	0.38	24								K—
4	C	37	Rectal stric.	Chr. act.	11 yrs.	5/23/38	10.60	3.40	7.20	0.47	38	x	—	?	11.0	4.8	36	3	W—
5	C	42	Rectal stric.	Chr. act.	10 yrs.	3/15/38	8.15	4.51	3.64	1.23	38	x	—	?					K d
6	C	35	Rectal stric.; genital elephanticiasis	Chr. act.	7 yrs.	5/19/38	7.85	4.51	3.34	1.35	45	x	—	—	11.3	3.6	36	2	W—
7	C	26	Rectal stric.; genital elephanticiasis	Chr. inact.	10 yrs.	12/9/37	9.63	4.10	5.55	0.74	45	x	—	—					K x
8	C	29	Rectal stric.	Chr. inact.	6 yrs.	1/6/38	8.83	3.92	4.91	0.80	38	x	—	1+					W x
9	C	36	Rectal stric.; rectal vaginal fistula	Chr. inact.	5 yrs.	1/22/38	9.71	3.84	5.87	0.65	38	x	—	1+					K d
10	W	36	Rectal stric.	Chr. act.	4 yrs.	2/3/38	9.22	3.68	5.54	0.67	30	?	—	—	9.2	3.3	30	1	W d
11	C	31	Rectal stric.	Chr. inact.	2 yrs.	2/1/38	10.10	3.48	6.62	0.53	30		—	—					K—
12	C	44	Genital elephanticiasis	2 yrs.	2/17/38	9.22	3.33	5.89	0.57	34	x	—	—	8.9	2.7	29	5	W—
						12/15/37	9.63	3.68	5.95	0.62	34	x	—	—					K—
						2/10/38	11.16	3.92	7.24	0.55	32	x	?	?					K—
						12/30/37	9.22	4.10	5.12	0.81	32	x	—	—					K—
						2/10/38	9.22	3.92	5.30	0.74	18		—	—					K—
						2/1/38	10.10	4.19	5.91	0.71	18		—	—					K—
						2/10/38	9.63	3.92	5.71	0.69			—	—					K—
						1/13/36	8.49	4.01	4.48	0.89					10.5	4.4		1	K—
						1/20/38	8.83	5.46	3.37	1.62	6		—	—					W—
						1/27/38	9.22	5.64	3.58	1.57			—	—					K—
						12/9/37	8.49	5.30	3.19	1.66	30	x	—	—					W—
						12/30/37	8.15	5.01	3.14	1.59			—	—					K x
						6/10/37	9.22	5.64	3.58	1.58			—	—					W x

13	C	25	Rectal stric.	Chr. act.	7 yrs.	12/22/36 2/ 5/37 2/ 8/37 5/ 5/37	9.63 10.60 11.16 10.10	3.61 3.60 4.29 3.84	6.02 7.00 6.87 6.26	0.60 0.52 0.62 0.61	11				9.3	4.0	35	2	K d W -
14	C	27	Rectal stric.	Chr. act.	3 yrs.	12/13/37 12/23/37	8.83 7.57	4.01 3.61	4.82 3.96	0.83 0.92	36	x			11.5	3.4	30	2	K -
15	C	27	Vulval ulcer	1 mo.	1/27/38 3/ 8/38	10.10 10.10	4.01 4.29	6.09 5.81	0.66 0.74	21	?			9.9	3.5	32	2	K x W -
16	C	30	Rectal stric.	Chr. act.	?	4/18/38 3/ 5/38	9.63 9.63	3.48 3.61	6.15 6.02	0.57 0.60	34	x			9.5	2.8	30	4	K x W x
17	C	22	Rectal stric.	Chr. act.	?	4/ 7/38 3/ 3/38	7.57 7.85	2.82 3.11	4.75 4.74	0.59 0.66	32	x			9.4	2.9	28	1	K - W -
18	C	25	Proctitis	Acute act.	6 mos.	1/27/38 2/ 2/38	8.15 8.15	4.10 4.29	4.05 3.86	1.01 1.11	41	x			12.4	4.5	37	2	K x W x
19	C	37	Proctitis	Chr. act.	3 mos.	3/10/38 2/ 3/38	8.15 9.63	3.29 3.76	4.23 5.87	0.78 0.64	36	x	?	1+	9.7	3.9	31	1	K x W x
20	W	34	Proctitis	Acute act.	3 mos.	2/17/38 3/ 3/38	7.07 6.84	4.51 4.40	2.56 2.44	0.64 1.81	19	x			11.2	4.2	20	3	K -
21	C	23	Rectal stric.	Chr. inact.	1 wk.	5/28/38 4/ 7/38	8.15 8.49	5.46 4.62	2.69 3.87	2.03 1.19	34	?			10.5	3.6	36	2	K x W x
22	C	27	Vulval ulcer	(?)	4/26/38 4/26/38	8.15 8.49	4.01 4.19	4.14 4.30	0.97 0.98	43	x			?	4.0	38	2	K - W -
23	C	31	Proctitis	Chr. act.	1 yr.	5/19/38 4/14/38	8.49 8.15	4.75 4.75	3.74 3.40	1.27 1.39	24	x			10.5	3.2	34	2	K -
24	C	31	Rectal stric.	Chr. act.	7 yrs.	5/12/38 6/11/38	8.15 8.83	5.01 4.10	3.14 4.73	1.59 0.87	30	x					26	2	K -
25	W	55	Rectal stric.	Chr. act.	15 yrs.	10/27/37 5/26/38	7.57 8.15	3.92 5.01	3.57 3.06	0.86 1.47	38	-			10.3	4.3	35	3	K -
26	C	39	Rectal stric.	Chr. act.	1 yr.	4/ 6/38 6/23/38	7.07 8.49	3.61 4.51	3.14 3.98	1.59 1.13	40				11.0	3.4	37	3	K -

TABLE 2.—Data on Men With Lymphogranuloma Venereum Studied at Vanderbilt University Hospital.

Number.	Race.	Age.	Diagnosis.	Activity.	Duration of disease.	Date of blood study determinations.	Total serum protein.	Serum albumin.	Serum globulin.	A/G ratio.	Sedimentation rate.	Costa.	Aldehyde.	Serum and water.	Hemoglobin.	Red blood cells.	Hematocrit.	No. of positive Papanicolaou tests.	Wassermann and Kahn.
1	C	62	Rectal stric.	Chr. act.	18 yrs.	2/7/38 2/9/38	8.49 8.15	3.22 2.91	5.27 5.24	0.61 0.56	18	?	—	—	8.0	2.9	24	2	K—
2	W	45	Rectal stric.	Chr. act.	5 yrs.	6/17/36	10.10	2.51	7.57	0.33	25	?	—	—	10.5 13.4	3.8 4.4	44	1	K—
3	C	25	Proctitis	Acute act.	18 mos.	1/19/38 2/11/38	9.22 8.83	4.29 4.01	4.93 4.82	0.87 0.84	25	x	?	?	9.0	2.9	28	2	K x W x
4	C	52	Genital, ele-phantiasis	...	9 yrs.	3/3/38 4/19/38	9.63 9.63	3.28 3.53	6.35 6.10	0.52 0.58	25	x	?	?				1	K x W x
5	C	25	Bubo	Healed	2 yrs.	3/1/38	8.15	5.15	3.00	1.73								1	W x
6	C	38	Bubo	Draining	1 yr.	12/20/37	8.83	5.64	3.19	1.77					12.0	4.7		1	K—
7	W	23	Bubo	Acute	6 wks.	1/31/38 2/3/38	8.83 8.15	4.75 4.67	4.08 3.48	1.16 1.35	47	x				3.8	37	2	W—
8	C	18	Bubo	Acute	1 mo.	12/8/37 1/3/38	7.85 8.49	4.10 4.75	3.75 3.74	1.09 1.26	16	—	—	—	14.0	4.7	44	3	K x W x
9	C	24	Bubo	Draining	3 mos.	3/10/38 12/7/37	8.49 9.63	5.01 5.15	3.48 4.48	1.44 1.15	25	x	—	—	13.1	4.5	42	2	K—
10	W	34	Bubo	Draining	5 mos.	3/8/38 12/17/37	8.15 7.31	5.01 5.46	3.14 1.85	1.59 2.94	3	—	—	?	14.0	4.5	44	1	W— K x
11	W	32	Bubo	Aspirated	6 wks.	2/25/38 3/10/38	7.57 7.85	6.44 4.75	1.13 2.56	5.75 1.86	31	x	—	—	13.5	3.7	42	2	W— K—
12	C	41	Bubo	Healed	2 yrs.	1/17/38 1/24/38	7.85 8.15	4.40 4.75	2.56 3.40	1.28 1.39	4	—	—	—	13.5	4.5	43	2	W— K—
13	C	28	Bubo	Draining	2 wks.	1/14/38 1/27/38	8.49 7.57	3.48 5.01	4.14 2.56	0.69 1.96	21	—	—	—	12.2	4.9	39	2	W— K—
14	C	18	Bubo	Resolved	1 wk.	2/21/38 4/26/38	8.15 7.85	4.01 4.88	5.01 2.56	0.69 1.96	14	—	—	—			46	2	K—
15	C	42	Bubo	Excised	1 wk.	6/11/38 3/22/38	7.31 7.51	4.62 3.92	2.69 3.59	1.73 1.09	20	x	—	—	11.6	3.1	39	1	K—
16	C	25	Bubo	Aspirated	1 wk.	4/16/38 3/12/38	7.85 8.49	5.30 5.15	2.55 3.34	2.04 1.53	19	x	—	—	10.6	5.0	44	3	K—
17	C	23	Bubo	Aspirated	1 wk.	5/2/38 3/10/38	8.15 9.22	4.75 5.15	3.40 4.07	1.40 1.27	22	?	—	—	11.0	4.3	39	2	K—

NASHVILLE GENERAL HOSPITAL CASES.

[illegible]

The blood was drawn without stasis. Two or more determinations were made in most of the V. U. H. cases, but not on the same day, because we wished to see what changes, if any, occurred during the course of the illness, especially in the acute stages. As normal values for the serum proteins we have taken those of Peters and Eisenman⁹ which are, for total proteins 6 to 8 gm. %, for albumin 4 to 5.5 %, and for globulin 1.4 to 3 %. Youmans, Bell, Donley and Frank¹³ found similar values for normal subjects in and around Nashville.

Sedimentation rate was determined by the Wintrobe method. Corrected rates of 20 mm. per hour for women and 9 mm. for men may be considered the upper limits of normal. The Costa reaction which has been used by one of us^{6a} in a previous study, was carried out in the usual manner.¹ Napier's⁸ technique was used for the aldehyde test, observation being carried out over the period of 1 hour. The "serum and water test" was done as recommended by Sia¹¹ for use in kala-azar, the readings being made during 1 hour.

The serologic diagnosis of syphilis was made by the Kahn test and by the Kolmer modification of the Wassermann test. In some cases, all of which were negative, the Kahn test only was done.

Hemoglobin determination and red blood cell counts were made in the usual manner. The Wintrobe tube was used in the hematocrit studies.

Results. The findings are summarized in Tables 1 and 2, which also indicate the nature of the lesions, so that the changes in the blood may be compared with the manifestations and duration of the disease. Of the total number of patients, 62 or 92.5% showed, upon at least one occasion, a total protein value of 8 gm. or over, which may be regarded as an elevation. If the value of 3 gm. or over is taken as definite elevation of globulin it was found that 62 (92.5%) of the cases showed this deviation from normal. As a result the albumin-globulin ratio was usually reversed. These changes in many cases are due not only to the elevation of globulin, but also to the depression of albumin values below the level accepted as normal, though, as will be stated below, we do not believe that lowered albumin levels are related to the disease.

Total serum protein and globulin values are summarized in Table 3. The findings are divided according to sex because of the relationship of the protein levels to the type of lesions which may be more or less sex related (this factor will be discussed below). In every case, at one time or another, the total protein was 7.5 gm. % or more. Among the V. U. H. cases the total protein was 8 gm. or more in 76.4% of the males and in 96% of the females. Total protein was above 8 gm. in all of the N. G. H. cases. Serum globulin was 3 gm. % or more in 82.3% of the males and in 96% of the females in the V. U. H. cases and in 100% of the males and in 95.2% of the females in the N. G. H. cases.

The data for the protein values are further broken down in Table 4, in order to show the relationship of serum albumin and globulin to each other. Of the 5 cases with total protein of less than 8 gm., none had a value of less than 7.5 gm. Serum albumin was less than 4 gm. in 17 cases (25.3%), the globulin being over 3 gm. Of those with

albumin values of 4 gm. or more, 73% of all cases, 6 had globulin values of 3 gm. or less.

TABLE 3.—TOTAL SERUM PROTEIN VALUES AND GLOBULIN LEVEL.

	Vanderbilt University Hospital.				Nashville General Hospital.			
	17 males.		26 females.		3 males.		21 females.	
	No.	%.	No.	%.	No.	%.	No.	%.
Total protein:								
7.5 gm. or more . .	17	100.0	26	100	3	100	21	100.0
8.0 gm. or more . .	13	76.4	25	96	3	100	21	100.0
Globulin:								
3.0 gm. or more . .	14	82.3	25	96	3	100	20	95.2

TABLE 4.—RELATIONSHIPS OF TOTAL PROTEINS, ALBUMIN AND GLOBULIN.

	Vanderbilt University Hospital.		Nashville General Hospital.	
	17 males.	26 females.	3 males.	21 females.
Total protein, 8.0 gm. or more:				
Albumin less than 4 gm. } . .	3	7	2	4
Globulin over 3 gm. } . .	10	17	1	16
Albumin 4 gm. or more }	1	..	1
Globulin over 3 gm. }
Albumin 4 gm. or more } . .	4
Globulin 3 gm. or less }
Total protein below 8 gm.:				
Albumin below 4 gm. }	1
Globulin over 3 gm. }
Albumin 4 gm. or more }
Globulin 3 gm. or less }

It is apparent that no case was found with hypoproteinemia. Further, that hyperglobulinemia is practically the only factor in the elevation of total serum proteins. The instances of depressed serum albumin are probably to be explained on other coincident factors.

The relationship of the total serum proteins, albumin and globulin to the type and activity of the lesions present is shown in Table 5.

TABLE 5.—PROTEINS RELATED TO TYPE AND ACTIVITY OF LESION.

	Total protein 8 gm. or more.			Total protein below 8 gm.		
	Albumin below 4 gm. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin 3 gm. or less.	Albumin below 4 gm. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin over 3 gm.	Albumin 4 gm. or more. Globulin 3 gm. or less.
Active rectal lesion:						
Acute	2	1	1
Chronic	12	21	1	1	1	..
Inactive rectal lesion . .	2	7
Chronic genital lesion . .	1	3
Inguinal bubo:						
Active	1	7	4
Healed	2

Rectal disease was present in 49 (73.1%) cases. Forty-eight (97.9%) of the 49 cases had total serum proteins, at least at one

time, of over 8 gm., and one had a total protein of over 7.5 gm. All but 2 also showed elevation of globulin to above 3 gm. Seventeen (34.6%) of the 49 had less than 4 gm. of serum albumin so that the hyperglobulinemia is actually more marked than seems apparent from the total protein values. The remainder had normal values for this fraction. In 40 of the 49 cases the disease was considered to be active and in 9 inactive. The activity of the rectal lesions bore no definite relationship to the degree of change in the serum proteins.

In 4 cases, chronic genital lesions only were present, 1 of these being a male with elephantiasis of the genitalia. All 4 cases had an elevation of the total serum proteins due to an increase of the globulin fraction. One had serum albumin of less than 4 gm.

Twelve patients had active buboes, either draining or in the stage of acute lymphadenitis. Two had healed buboes. Elevation of globulin was not as great in patients with buboes alone as in those with chronic genital and rectal lesions. Of the 12 patients with active bubo only 8 (66%), had a serum globulin above 3 gm. One had an albumin below 4 gm. In the 2 patients with healed bubo, infection had occurred 2 years before. They presented ragged inguinal scars, a history compatible with lymphogranuloma venereum and markedly positive Frei tests. Both of these showed a serum globulin of 3 gm. or more, and a total protein of over 8 gm. % the albumin fraction being normal.

Sedimentation Rate. Because it is generally believed that changes in the sedimentation rate are related to alteration in serum proteins, this test was done in 39 of the 43 V. U. H. cases (Tables 1 and 2). Increased rate, though slight in some, occurred in 21 of the 25 females in which the test was done, and in 12 of the 14 males. One of the 2 males with normal rate had had a bubo 2 years before.

It is noteworthy that there was no correlation between the degree of increased rate and the amount of hyperglobulinemia. In the female group were cases with marked increase in serum globulin but with normal sedimentation rates. It is possible that there may be some relationship between the sedimentation rate and activity of the lesion. This is indicated by the fact that practically all the male cases which had active buboes showed an increased rate.

Costa Reaction. This test, also possibly related to serum proteins or their derangements, was carried out in 37 of the 43 cases studied at V. U. H. (Tables 1 and 2). As may be seen from the tables, the results rather closely paralleled those of the sedimentation rate, though the test is probably not quite as sensitive, as suggested by the experience of one of us (R. H. K.) with the test in tuberculosis. In the present study, the Costa test was negative in 5 cases where the sedimentation rate was increased, though in 2 of these there was very slight increase in sedimentation rate. The Costa reaction was questionable in 5 cases in which the sedimentation rate was increased. Among 5 cases with a negative Costa reaction there were 3 in which

there was definite elevation of the serum globulin. Therefore, as in the case of the sedimentation rate, there was no correlation between the degree of protein derangement and a positive or negative Costa reaction.

Aldehyde Test. A positive aldehyde test, as described by Napier in untreated kala-azar, was not obtained in any of the 34 cases in which it was done. Opaque solidification of serum never occurred even after some hours. In 5 cases, all showing hyperglobulinemia, the test was recorded as questionable. In such cases, the serum jellied and was slightly cloudy after 30 minutes or more. Napier described this as occurring in some cases of tuberculosis, leprosy and malaria.

Serum and Water Precipitation Test. This test was also carried out in 34 cases, with observations at 5, 15, 30, and 60-minute intervals. In no case did a sediment form which Sia described as a definitely positive test. At the end of an hour, in 4 cases, a haziness was found, and the test was recorded as a 1+. Hyperglobulinemia was present in all those patients who showed a 1+ test, and in 5 of those with questionable ones.

Wassermann and Kahn Tests. Because of a possible relation of these tests to the globulin fraction of the serum proteins and because Gutman and Williams found the Wassermann reaction to be anti-complementary in 22% of 74 Frei positive cases, the results in our cases are of interest.

Of the 43 V. U. H. cases, none were found to have anti-complementary Wassermann reactions. Both Wassermann and Kahn tests were negative in 13 cases, and both positive in 9 cases. The Kahn test alone was negative in 16 additional cases. Both tests were doubtful in 1 case, the Wassermann was negative and the Kahn doubtful in 2 cases, and the Wassermann negative and Kahn positive in 2 cases.

In the N. G. H. group of 24 cases, the Wassermann test was negative in 19 instances, positive in 4, and not done in 1.

Recently, one of us^{6b} reviewed the cases of rectal stricture treated in V. U. H. since 1926. Most of these cases were not proven by the Frei test, but analysis of the history and physical findings made it seem reasonable that a certain percentage of these were due to lymphogranuloma venereum. In those selected as probably being cases of this disease, the Wassermann reaction was negative in 29 and positive in 16, 2 were Wassermann and Kahn positive, 6 were Wassermann negative and Kahn positive, 1 was Wassermann doubtful and Kahn positive.

Our findings do not agree with those of Gutman and Williams as regards the frequency of anti-complementary Wassermann reactions in lymphogranuloma venereum. (Since this study was completed an anti-complementary Wassermann and positive Kahn test were found in a patient with bubo and hyperglobulinemia.)

Hemoglobin, Red Cell Counts and Hematocrit Studies. A study of the tables indicates that secondary anemia is frequent among the patients suffering from active forms of lymphogranuloma venereum. This is especially true in females in whom anemia was greater than in males, and more frequent. In fact practically no female was found with a normal hemoglobin and red cell count. It should be pointed out, however, that chronic manifestations of lymphogranuloma venereum, such as proctitis or rectal stricture, are not the only possible causes of this anemia. Secondary anemia is generally not uncommon among our clinic patients, especially among females, in whom childbearing and poor diet lead to an iron deficiency.

These examinations were carried out not because we expected to find any definite relationship of the state of hemoglobin, red cells or hematocrit reading to the disease under consideration, but to satisfy ourselves that the hyperproteinemia was not related to dehydration and blood concentration. To be sure, this did not have to be considered seriously because of the almost constant hyperglobulinemia. (White blood cell counts are not given since they showed only the usual changes which occur in lymphogranuloma venereum.)

Non-protein Nitrogen. In a small number of cases with hyperproteinemia the non-protein nitrogen was determined. In no case was it found to be elevated.

Discussion. Hyperproteinemia due to hyperglobulinemia is not specifically restricted to lymphogranuloma venereum. It has long been known that increase in the serum proteins may occur in a number of diseases, aside from those due to dehydration alone. Multiple myeloma has been recognized as a cause of hyperglobulinemia. (Incidentally no Bence-Jones protein was found in those of our cases of lymphogranuloma venereum so tested.) Kala-azar is associated with hyperglobulinemia. Liver disease also may cause an abnormal elevation of serum globulin. Peters and Eisenman⁹ found increased globulin in ulcerative pulmonary tuberculosis, and in syphilis, especially of the gummatous types.

It is apparent that the elevation of serum globulin to above normal levels, with an abnormally high total protein in those whose albumin is normal, is a frequent occurrence in the various stages of lymphogranuloma venereum.

The likelihood of a dietary deficiency causing a drop in albumin in many of these patients is supported by the frequency of anemia in the women. However, a study of the tables indicates that the globulin elevation is not compensatory for the drop in serum albumin because the latter was not lowered in the majority of the chronic cases and in almost none of those with buboes. Also it will be noted (Tables 1 and 2) that with the elevation of the total serum proteins there is a corresponding increase in serum globulin in most cases without a lowering of the albumin fraction, again indicating that the increase in globulin does not occur as a compensatory reaction.

It is worthy of emphasis that protein derangement occurs not only in the presence of rectal disease, but also in association with other lesions due to the disease. Therefore, the rectal or bowel lesions have no exclusive relationship to abnormalities in the serum proteins.

Elevation of serum globulin may appear early in the disease, as shown in Case 7 (Table 2), a young white male seen in the stage of bubo, in whom the protein change occurred before the Frei test became positive. It also may persist for many years, if not permanently, as may be seen from Tables 1 and 2 where the duration of the disease is recorded. Furthermore, the increase in globulin tends to become greater as time passes, and the highest values are found in cases of years standing. Apparently the derangement persists with what appear to be completely healed lesions.

The change in the proteins is not related to the activity of the lesion, though the globulin level is less often as high in active bubo cases as in cases with lesions of many years' duration. Possibly this means the disease has not been established sufficiently long enough for the maximum change to have taken place.

We offer no explanation as to the possible cause of the derangement of the serum proteins which we observed. As a control for the involvement of lymphatic tissue, we have made serum protein determinations in a number of cases of chancroid with bubo, and of secondary syphilis with especially extensive lymphoid involvement and have found no instances of changes in the protein fractions. However, we are aware of the case of a female negro child in whom there was proven tuberculous lymphadenitis and hyperglobulinemia. In light of the fact that lymphogranuloma venereum as another genito-infectious disease is not infrequent in syphilitics, some of the examples of hyperglobulinemia which have been reported in the past as occurring in syphilis may well have been due to coincident lymphogranuloma venereum.

Though the hyperproteinemia due to hyperglobulinemia in lymphogranuloma venereum is not a specific finding, it is a very constant finding and so is of some diagnostic value. Further, it is a remarkable fact that derangement of proteins persists for many years, and is probably a permanent change. Whether this indicates persistent infection cannot be determined at this time.

Summary. 1. Blood studies in 67 cases of lymphogranuloma venereum have been presented.

2. At one time or another 62 cases showed a total serum protein of 8 gm. or more, and in 62 the serum globulin was 3 gm. or more.

3. Derangement of the serum protein occurs at any stage of the disease and apparently persists permanently. Such changes occur in cases of buboes, chronic genital lesions, and in acute and chronic proctitis as well as in rectal strictures.

4. Other tests possibly related to serum proteins show either no changes or inconsistent changes.

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STUDIES ON THE PHYTOTOXIC INDEX.

III. AN EVALUATION OF THE METHOD WITH REFERENCE
TO DEPRESSED PSYCHOTIC PATIENTS.

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In previous investigations by use of the phytotoxic method of Macht⁴ we obtained results which disagreed with those of other workers. We found that the blood and urine from male schizophrenic patients who were otherwise healthy were not more toxic to *Lupinus albus* seedlings than were the blood and urine from normal, healthy men^{1a} and that the phytotoxicity of the blood of normal, healthy women did not vary materially whether taken during the inter-menstrual or intra-menstrual periods.^{1b} These findings were at variance with those of Tscherkes and Mangubi⁸ and Macht and Lubin.⁵ These discrepancies led us to make a careful study of all the variables concerned in the obtaining of the phytotoxic index. To obtain this information we have determined the rate of growth of the *Lupinus albus* seedlings and also the effect of the initial root length and various temperatures on the index. The variation in toxicity of blood serum at different concentrations and the minimum number of seedlings necessary to give a statistically valid test were also determined.

As one of us (J. M. L.) in an earlier study in collaboration with Macht⁵ had found that the serum of depressed patients was toxic to the *Lupinus albus* seedlings, it was decided to use depressed patients in the present study.

Method. Ten male patients were selected and paired with an equal number of normal male subjects. The selections were made by the attending psychiatrist on the basis of the depth of the depression and only those showing severe depression were utilized. Inasmuch as other workers have reported that pernicious anemia³, pemphigus,⁶ and otosclerosis⁷ caused an increase in blood phytotoxicity, no patient was chosen who had any indications of these diseases. The group therefore represented as nearly as possible a sample of depressed psychotic patients without complicating organic diseases.

Because the "phytotoxic index" depends on the rate of growth of the root tip of the *Lupinus albus* seedling, it is essential that the data be collected in such a way as to permit control of the inherent biologic variables. Macht and his followers used a 1% solution of the test substance in a 50% strength of Shive solution.^{4,8} No information is available to indicate that this is the optimal concentration. The ideal dilution is one which contains the minimum amount of the test substance which will yield a quantitatively significant index.

We have modified the technique to afford better control than in the original method. Each blood sample was defibrinated and diluted with water to make three different concentrations, and then mixed with an equal volume of Shive solution. The final blood dilutions were: $\frac{1}{2}$ %, 1%, and 2%. The phytotoxic index for each patient per blood concentration was obtained using 25 test seedlings for each series. From these figures the phytotoxic-index means of the entire group per strength of blood solution were obtained. The means were 0.871 ± 0.018 , 0.853 ± 0.014 , and 0.590 ± 0.010 respectively, and the corresponding standard deviations were 0.136 ± 0.013 , 0.157 ± 0.010 , and 0.093 ± 0.007 .

By the criterion of the standard error, the difference between the means of the $\frac{1}{2}$ % and the 1% strengths was not significant. On the other hand, the difference between the mean of the 2% solutions and the means of either the 1 or $\frac{1}{2}$ % was significant. It is apparent that the toxic action of the blood is slight in the lower concentrations and that 2% is the minimal strength necessary to retard appreciably the rate of growth. We therefore used 2% solutions for all our tests.

In order to study the variability of the seedlings in the same solution the mean root growth was determined when different numbers of seedlings were used. It was found that in order to have an adequate representation of different growth types and thus minimize the inherent variability between tests, it was necessary to have at least 20 seedlings in each test. Our studies were therefore run on the basis of 25 seedlings to allow for occasional spoiling of certain tests by broken seedlings or complete failure to grow.

In order to determine the effect of initial root length in the test, the rate of growth was determined by the following procedure.

Twenty-five seedlings were placed in moss for germination. They were examined every 12 hours until the roots had definitely started growth, which in the majority of instances, required 48 hours. The seedlings were then placed in half-strength Shive solution exactly as in the actual tests. The root lengths were measured and recorded every 12 hours until branching occurred, which was roughly around 8 days. The room temperature was generally recorded once a day.

A growth curve of the Gompertz type, $Y = 14(1.07)^{0.52x}$, was calculated from the data thus obtained and gave a good fit to the observed values. From this curve (Fig. 1) it is noted that the steepest portion and therefore the most rapid growth occurred shortly after the roots obtained a length of 2 cm. The growth from this point to about 7 cm. appeared to be at a uniform rate and then there occurred a gradual decrease in the rate of growth as indicated by a flattening of the curve. It is evident, therefore, that seeds

should be chosen for testing so that their lengths will fall between these limits during the test. Furthermore, the seeds should be so distributed that the means of the root lengths of each series being tested should be equal to that of the Shive control. The average initial length of the roots taken in the test was 3.07 cm., and in no case were tests made with beans of an average root length of less than 2.0 cm. We can state, therefore, that the tests were conducted on beans at such a stage of growth that the curvature at the extremes of the growth curve was not an important factor in the final result.

Further precautions were taken. The technician, during her menstrual periods, used rubber gloves to prevent palmar perspiration contaminating the seedlings.^{1b} The technique was performed by the same person during the entire study.

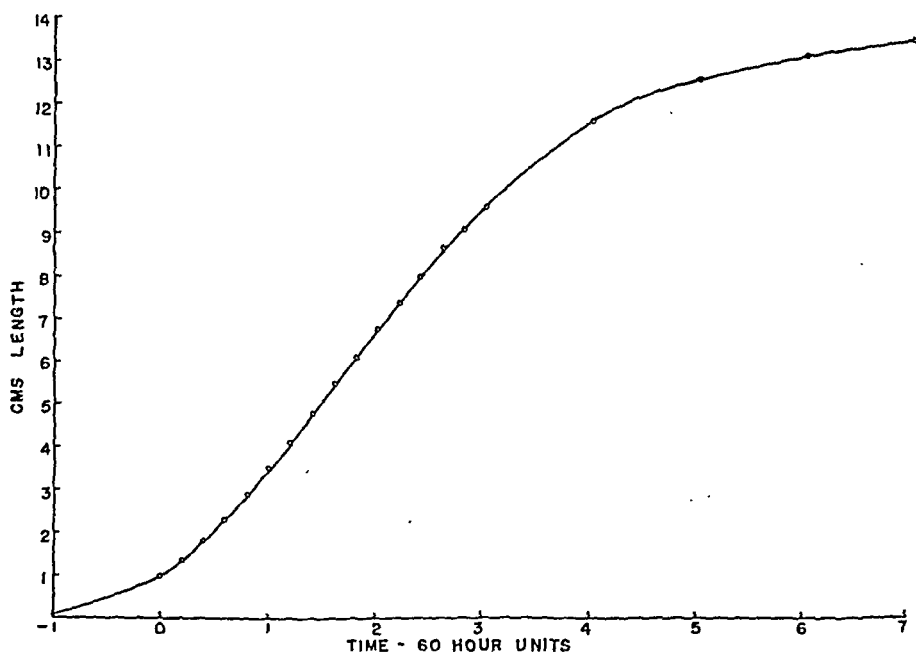


FIG. 1.—Gompertz curve $Y = 14(1.07)^{0.52x}$ fitted to growth of *Lupinus albus* seedlings, 20° C.

In previous studies most investigators have not run normal serums at the same time as their test serums but have taken the value of 70 to 80% as the phytotoxic index of normal blood serum. As the tests are run at room temperature the possibility arises that tests run during warm weather may not give the same results as those run during cold weather because of a differential effect of the toxic materials on the root growth at different temperatures.

In order to investigate this possibility, the 10 pairs of patients and normal subjects were tested against Shive solution under different conditions of temperature and initial root length. The seedlings were divided into two groups, one having long roots and the other having short roots. Since all the short roots were not of exactly the same length, we get grouping into lengths within each

major group. These groups were then distributed into six divisions containing 25 beans in such a way, however, that the average length of roots in each division was approximately the same for the patients, normal subjects, and Shive solutions in both the warm and cold temperature groups. Thus the 6 shortest beans were assigned to warm and cold temperatures for patient, control, and Shive solutions, then the next 6, and so on until all the beans were distributed. Because of occasional failure of some of the beans to grow or because of accidents, and so on, it was not possible to obtain 25 seedlings in each set and the final analyses were made on the results from 18 seedlings.

A test of depressed patient, control, and Shive's solution were always run simultaneously and form what we shall call a set. Each set was run at different times and on a different lot of beans. While these lots were not of exactly the same length, or possibly inherent growth capacity where the temperature conditions of the experimental chamber were the same from set to set, the lots were the same for the 3 members of each set. From set to set the short roots averaged initially from 1.7 cm. to 3.9 cm. length, while the long roots averaged 3.5 to 5.8 cm. This lack of consistency was due to inherent difficulty of obtaining uniform growth in the germinating seeds, and introduced some uncontrolled variation between the sets. The roots assigned to long and short groups did not differ in length to the same extent for all sets. The average difference between the long and short groups varied from 1.1 cm. to 1.9 cm. The temperature of the cold room varied between 15° and 20° C. while that of the warm room varied between 26° and 35° C.

TABLE 1.—AVERAGE GAINS IN ROOT LENGTH PERTAINING TO BEAN SEEDLINGS GROWN IN PATIENT BLOOD, CONTROL BLOOD, AND SHIVE NUTRIENT SOLUTION; 18 ROOTS AT EACH OF TWO TEMPERATURES AT EACH OF TWO LENGTHS FOR EACH OF 10 PATIENTS, 10 CONTROLS, 10 SHIVE SOLUTION.

	Short.				Long.			
	Warm.		Cold.		Warm.		Cold.	
	Mm.	P.I.	Mm.	P.I.	Mm.	P.I.	Mm.	P.I.
Patients . . .	6.20	92.7	4.28	93.8	4.87	89.0	4.25	109.0
Controls . . .	5.62	84.0	4.01	88.9	4.52	82.4	3.84	98.7
Shives . . .	6.69	..	4.51	..	5.47	..	3.89	

The average gains in root length for patients, controls, and Shive's solutions for each temperature and each length separately and the phytotoxic indices arising from these values are given in Table 1.

The increase in root length varies significantly from one set of roots to the next both in respect to initial root length and temperature. We find that for any given set where the ranges of lengths are small, the initial root length is relatively unimportant in determining the subsequent gain, but that where great differences in initial length occur as between long and short sets, the final gain is significantly influenced by this factor. Thus the average difference in gain for all sets between long and short roots is 0.74 mm. The

difference is more marked in the warm room where the short roots gained an average of 1.22 mm. in excess of the long roots, than in the cold room where the difference is only 0.27 mm.

The effect of temperature is even more marked than that of initial length, the average gain in the warm room being 1.44 mm. more than in the cold room. In this case, too, the short roots were affected more than the long ones, as the average difference for the short roots is 1.92 mm. while for the long roots it is 0.95 mm. Both of these differences are highly significant, as is the difference between the effects amounting to 0.97.

The phytotoxic index shows great variation from set to set, the highest index for both patients and normal subjects being obtained for long roots in the cold room, and the lowest for long roots in the warm room. Even for short roots the index is higher for those growing in the cold room though here the difference is slight. It is apparent, therefore, that the phytotoxic index is not constant as the effect of temperature causes a more marked effect on the seeds growing in Shrive solution than it does on those growing in blood. Furthermore, the index for normal individuals is not 0.75 as given by Macht but varies from 0.99 to 0.40¹ depending on the conditions under which it is obtained. There is no consistency in the average difference in growth between Shive and blood from set to set so that the mean difference of 0.45 mm. cannot be regarded as significant. Furthermore the rate of growth of the seeds was greater in the patients' bloods than in the control blood, although the difference between them, 0.39 mm., is not significant. However, if we compare the growth of the long roots for the patients in the warm room with that of the control subjects in the cold room we obtain a difference of 1.03 mm. in length and 10.3 in the phytotoxic index, and these differences are significant.

From these results it would appear that the assumption that change in the variables of temperature and root length would affect the rate of growth of the seedlings in Shive solution to the same extent as those in the test solutions, and therefore the phytotoxic index would not be altered, cannot be maintained. It is evident, therefore, that no comparison as to toxicity can be made between two groups of subjects by means of the growth of *Lupinus albus* seedlings, unless they are studied with an adequate number of seeds—at least 20—under identical conditions of temperature, root length, and seed lot.

Summary. A study was made of the factors influencing the growth of *Lupinus albus* seedlings used in the phytotoxic index of Macht, using bloods taken from normal and depressed psychotic male subjects. It was found that the effect of variation of temperature and initial root length was not of the same magnitude on the roots in straight Shive solution as compared with those in Shive solution containing 2% of blood.

The phytotoxic index of normal individuals was found to vary from 0.40 to 0.98, that of depressed patients from 0.89 to 1.09.

Cold environment was found to retard seeds growing in Shive solution more than those growing in blood and to have a greater effect on long roots than on short ones.

Conclusions. 1. No comparison of phytotoxic indices is valid unless the tests are made with at least 20 seedlings in each set of Shive solution, control solution, and test solution, and the initial root lengths and other conditions of growth are matched in each set.

2. The phytotoxic index of normal subjects is not constant and cannot be given as 0.75 as stated by Macht.

3. The toxicity of blood from depressed patients is not greater than that of normal subjects.

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THE ELECTROCARDIOGRAM DURING INSULIN SHOCK TREATMENT OF SCHIZOPHRENIA AND OTHER PSYCHOSES.

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THAT hypoglycemic shock may have an effect on the heart and circulation has been established by many observers. This conclusion is the result of studies of the effect of moderate grades of hypoglycemia on patients having varying grades of myocardial disease. The increasing use of extreme grades of insulin shock in the treatment of schizophrenia and allied disorders makes it important to review the cardiac effects of this therapy not only in the presence of myocardial disease but in normal hearts as well.

Previous electrocardiographic studies during insulin shock, made chiefly in the presence of myocardial disease, have revealed inversion of the *T* waves, extrasystoles, auricular fibrillation, disturbances

in the auriculo-ventricular condition and lengthening of the QT interval.^{10,11,17,21-23}

Studies on the electrocardiographic effects following insulin shock treatment in schizophrenia are relatively few and largely confined to foreign literature. Hadorn⁹ and Bieglbach and Dussick³ have observed depression of the ST intervals, flattening and inversion of the T waves prolongation of the QT interval and extrasystoles.

The object of this presentation is to record the electrocardiographic findings in 40 patients in whom 58 studies were performed during insulin shock therapy. These studies were made in young subjects of mental disorder, chiefly between the ages of 20 and 30. Before acceptance for this type of therapy, these patients were submitted to a complete physical examination including an orthodiagram and one or more control electrocardiograms. Only patients with normal electrocardiograms and negative cardiac findings were accepted for this study. On the day of this study, the patients were given a dose of insulin, ranging from 35 to 340 units. Electrocardiograms with simultaneous blood sugars were taken at varying periods of time, usually 3, 4 and 5 hours after insulin administration. In most instances, the patients were in coma at the time the electrocardiograms were taken; a tracing was taken at the termination of the coma. In those cases that showed electrocardiographic changes, successive tracings were taken during the day until the tracing returned to a normal form. The tracings were obtained during various stages of shock therapy which was continued 6 times a week for approximately 8 weeks.

TABLE 1.—AGE, SEX AND TYPE OF MENTAL DISORDER.

Age.	Cases.
10 to 19	12
20 to 29	21
30 to 39	7
Total	40

The sexes were equally divided. In this series, there were 35 cases of dementia precox, 4 were manic-depressives and 1 patient had paresis.

Insulin Dosage. The usual routine of therapy was to start each patient with 20 units of insulin on a fasting stomach and increase the dose 10 units daily until the patient went into hypoglycemic coma; this usually occurred within 3 hours after the administration of insulin, if the dosage was adequate. The determination of the state of "coma" was made arbitrarily by the inability of the patients to respond to such stimuli as shaking, pin-prick, and so on, and also the findings of loss of swallowing or corneal reflexes. Usually this was obtained with an average dose of 90 units of insulin. Some cases, however, required as high as 340 units (Case 10) to produce

this state. They were kept on this shock dose during the remainder of the period of treatment.

The Blood Sugar During Insulin Shock Therapy. The initial effect of an adequate amount of insulin was seen $\frac{1}{2}$ to $\frac{3}{4}$ of an hour following injection and the maximum fall in the blood sugar was observed in 2 to 3 hours. Blood sugar values of less than 20 mg. per 100 cc. were unusual at this point; the usual range in our series was between 20 to 35 mg. per 100 cc. There then occurred a gradual rise in the blood sugar even though the patient was not given carbohydrate. This is presumably due to the compensatory action of adrenalin. There is no necessary relation between the depth of coma and the level of the blood sugar. Patients may remain in coma or develop deeper coma in spite of a gradually rising blood sugar.

TABLE 2.—SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS.

<i>Depression of ST segment:</i>		Cases.
ST1, 2 and 3		1
ST1 and 2		4
ST2 and 3		12
ST1		1
ST2		4
Total		22
<i>Changes in the T waves:</i>		
Low T1		3
Low T2		2
Prolonged QT interval		6
<i>Arrhythmias:</i>		
Auricular fibrillation		2
Auricular extrasystoles		1
Shifting pacemaker		2
Total		38
<i>Minor Changes.</i>		
<i>Arrhythmias:</i>		
Sinus arrhythmias with other changes		8
(alone in 5 cases) Total		13
Sinus bradycardia		4
(alone in 2 cases) Total		6
Sino-auricular block		5
<i>P waves:</i>		
Split P2		2
Inverted P2 and 3		1
Total		3
Slurred QRS complexes		2

Electrocardiographic Changes. Alterations in the electrocardiogram more or less marked were obtained in 38 of 59 shock treatments (60%). These are detailed in Table 2. The significant changes are as follows: 1, depression of ST segment; 2, flattening of the T waves; 3, prolongation of QT interval; 4, arrhythmias; auricular fibrillation, auricular extrasystoles, shifting pacemaker and sino-auricular heart block; 5, P wave changes and slurring of the QRS complexes.

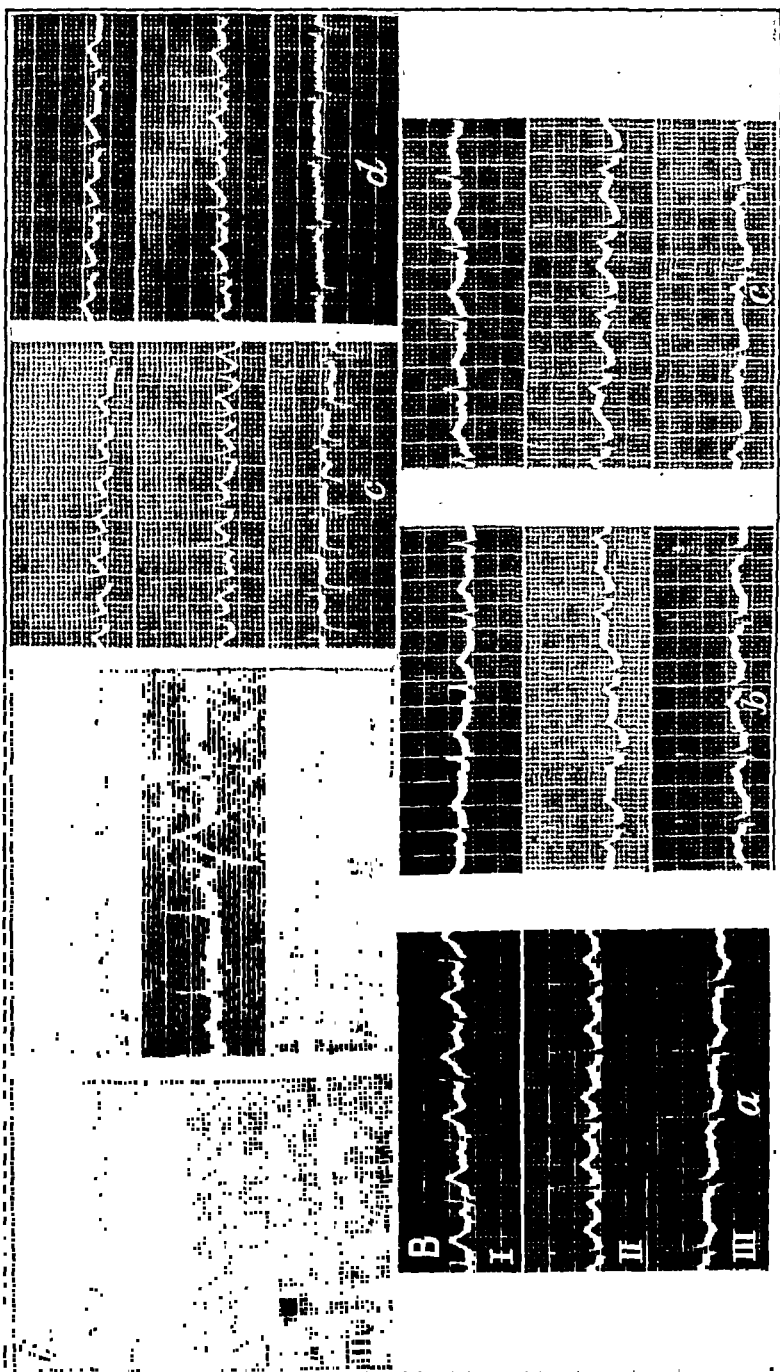


FIG. 1A.—Case 18, aged 31, male, dementia precox, paranoid. (a) Control, 1/22/37, 4 p.m. normal tracing. This patient received 75 units of insulin at 7:30 A.M., 5/23/37. (b) 11:20 A.M. patient in coma. Blood sugar 15 mg. %. Auricular fibrillation is present with occasional ventricular extrasystoles. Average rate, 75 per minute. This patient's coma was terminated at 12:45 p.m. (c) 4 p.m. Auricular fibrillation persists, rate averages 160 per minute. Patient manifested no symptoms of cardiac embarrassment. (d) 5/24/37. 11 A.M. normal rhythm.

FIG. 1B.—Case 35, female, aged 20, dementia precox, catatonic. (a) Control 12/6/37, 4 p.m. normal tracing. This patient received 140 units insulin at 7:30 A.M., 12/7/37. (b) 11:30 A.M. blood sugar 22 mg. %. Patient in coma. Note depression of ST intervals in Leads II and III. (c) 12 noon blood sugar 26 mg. %. Patient in coma. Note depression of ST2 and 3 and long QT interval in Lead II. This tracing returned to normal that afternoon at 4 p.m.

No changes were observed in 7 shock treatments besides sinus arrhythmia or sinus bradycardia. The latter is not to be regarded as an important change. No electrocardiographic changes were observed in 13 shock treatments. We can, therefore, state that no significant electrocardiographic changes were obtained in 20 of the 58 treatments (35%).

The most marked electrocardiographic changes were recorded usually during the period of the lowest blood sugar levels; but few exceptions were observed. In most instances, the changes returned to normal with return of the blood sugar to normal levels. In some, however, it took 2 to 3 hours for these changes to disappear. In 2 cases which developed auricular fibrillation, 1 returned to normal rhythm within 4 hours, and the other within 24 hours. In none of our cases were the changes permanent. Hadorn⁹ has noted some instances, however, where the changes have not been reversible.

Discussion. In view of the profound changes in the organism as a whole during severe hypoglycemia in which the heart muscle must participate, it appears almost inevitable that electrocardiographic changes should be recorded. The presence of the electrocardiographic changes noted above are usually considered evidence of some derangement in the myocardium, either toxic or the result of disease. Their reversible character in these patients would suggest that whatever is the cause of the disturbance in the heart, it is transient in nature.

The insulin shock treatment above described produces profound alterations in the chemistry of the body, some of which will be described presently. We feel that all of the systemic alterations to be mentioned could be possible factors in causing the electrocardiographic changes described. Whether or not they are the actual cause of these changes we cannot definitely state; however, in a discussion of the possible factors responsible for the electrocardiographic changes, the following should be taken into consideration.

1. *Hypoglycemia*.^{*} The blood sugar falls to an extremely low level in these patients (10 to 35 mg. per 100 cc.); frequently there is no available glucose in the blood stream. The patient remains in the hypoglycemic state for about 4 to 5 hours. A depletion of the glycogen store takes place first in the liver, then in the muscles and finally in the heart. In addition, the work of the heart is increased; the minute volume is increased 15% to 45%.^{3,6,15} This increased work has been ascribed as resulting from a compensatory discharge of adrenalin. Peripheral dilatation is indicated by the presence of capillary pulsation.⁶ Since oxygen consumption is increased in hypoglycemia, the bright red color and high oxygen content of the venous blood is evidence of a more rapid blood flow. The pulse

* The increased cardiac output, the increased pulse pressure and other circulatory phenomena indicate that insulin hypoglycemia does not produce circulatory shock in its usual sense.

rate is accelerated; the systolic pressure may be elevated and there is an average increase in pulse pressure of 73%. According to the figures of Cruickshank and Patterson,⁴ the normal heart utilizes

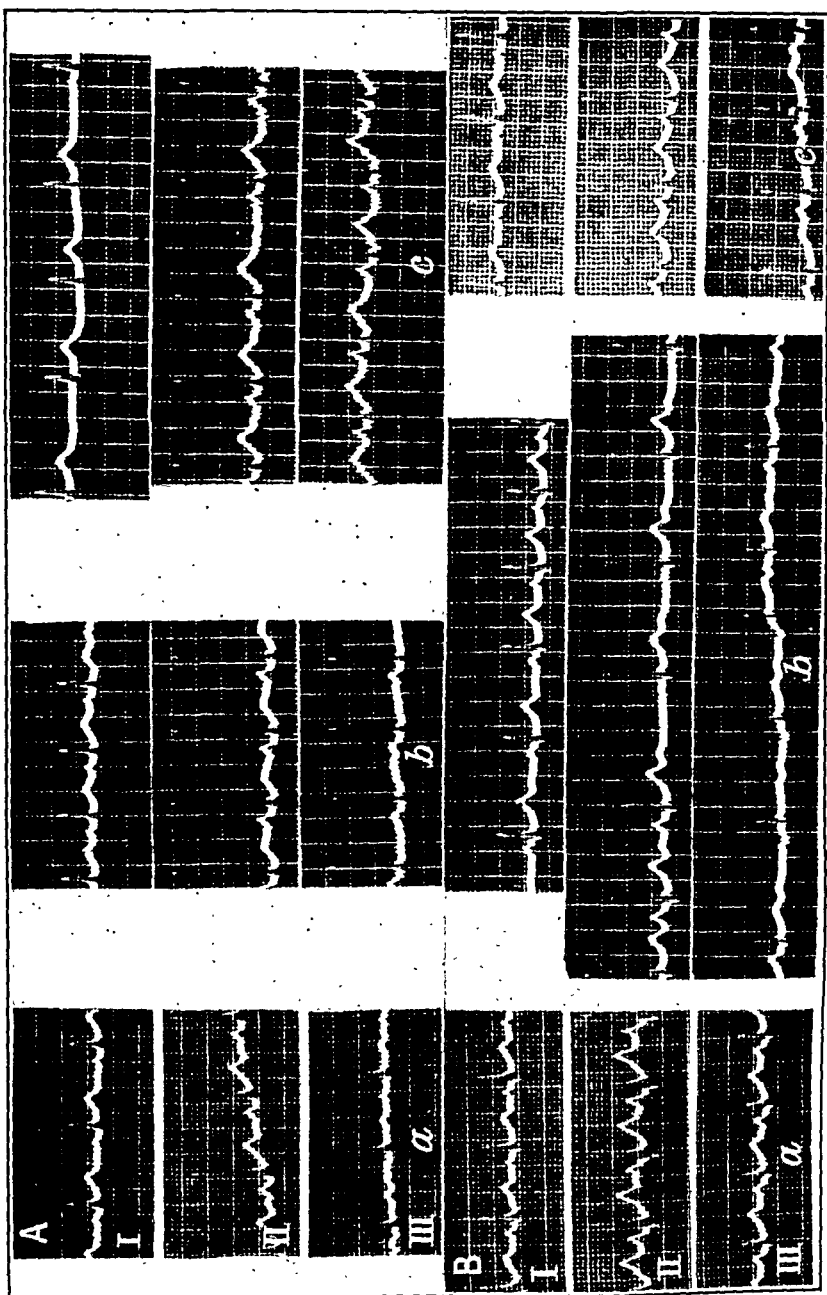


FIG. 2A.—Case 2, aged 26, male, dementia precox, paranoid. (a) Control 11/29/37. 4 P.M. normal tracing. The patient received 100 units insulin at 7:30 A.M., 11/30/37. (b) 11:05 A.M., blood sugar 22 mg. %. Patient in coma. Note depressed ST₂ and 3 and long QT interval. (c) 12:05 P.M. in coma. Note presence of sinus arrhythmia and lower ventricular rate.

FIG. 2B.—Case 30, aged 30, male, dementia precox, paranoid. (a) Control 11/8/37. 4 P.M. normal tracing. This patient received 130 units insulin at 7:30 A.M., 11/9/37. (b) 11 A.M., blood sugar 26 mg. %. Patient in coma. Note bifid P₁ and 3; change of pacemaker in Leads II and III, accompanied by change in rate. (c) 12:05 P.M., patient had been terminated 5 minutes before. Note depression of ST₁, 2 and 3 and prolonged QT in Leads II and III.

1.87 mg. of sugar per gm. per hour. Thus with increasing demands for effort come decreasing supplies of available energy in the form of combustible glucose.

2. *Dehydration.* During the course of a single shock treatment, these patients may lose as much as 5 pounds of water; there results consequently a marked hemoconcentration. The blood volume is diminished, particularly the plasma volume.³ There is a rise in the erythrocyte, hemoglobin and hematocrit values. The changes reported are large enough to affect concentration of electrolytes and non-electrolytes of the blood.¹⁴

3. *Alteration in Electrolytes.* Marked disturbances in electrolytes have been observed. There is an increase in the pH of the blood with a tendency toward alkalosis; the potassium content of the serum falls and the sodium content rises; the serum calcium rises slightly or is constant; the magnesium is not uniformly affected; the inorganic phosphates decrease and a decrease in chlorides has been reported.^{1,3,8}

4. *Effect of Insulin per se.* The administration of insulin *per se* has been said to be responsible for some of the electrocardiographic changes observed. Studies by Schaffer, Bucka and Friedlander,²¹ von Haynal, Vidovsky and Györgi,¹¹ and Soskin, Katz, Strousse and Rubinfeld²² have been reported in which the administration of insulin immediately covered by sufficient glucose to prevent hypoglycemia in a patient with cardiovascular disease also resulted in electrocardiographic changes. These alterations have been ascribed by these workers to the direct effect of insulin upon the myocardium. It is extremely difficult to dissociate the direct effects of insulin and those due to its hypoglycemic effects in the experiments of the above type, since one cannot be certain that the absence of hypoglycemia in the peripheral blood by the administration of glucose mirrors exactly the conditions surrounding the tissues of the heart. For this reason we doubt whether the electrocardiographic changes can be ascribed to a direct insulin effect upon the myocardium.

5. *Anoxemia.* It has been shown that a similarity exists between the effects of hypoglycemia and those of oxygen deficiency produced by inhalation of gas mixtures. The investigations of Holmes,¹³ Wortis,²⁴ Dameshek and Myerson⁵ and Himwich¹² and his collaborators suggest that lowering the blood sugar reduces the oxygen consumption of the brain and that oxidation in this organ is lowered when the supply of either oxygen or dextrose is reduced. This statement does not apply to an equal degree to the heart which can metabolize proteins and fats. However, the lack of available carbohydrate and the increased work of the heart during hypoglycemic shock of long duration would suggest that anoxemia may be a factor in producing the cardiac effects. The *ST* interval changes produced are similar to those observed by Rothchild and Kissin¹⁹ and others after experimental anoxemia in the human subject.

6. *Cerebral Alterations.* Profound changes occur in cerebral metabolism during hypoglycemia and the resultant coma. It has been fairly well established that the heart may be indirectly affected by alterations in the brain. That profound functional alterations

occur in the metabolism of the brain cells during hypoglycemia has been established; it is the basis of the insulin shock therapy. These changes may be responsible in part at least, for some of the electrocardiographic alterations observed.

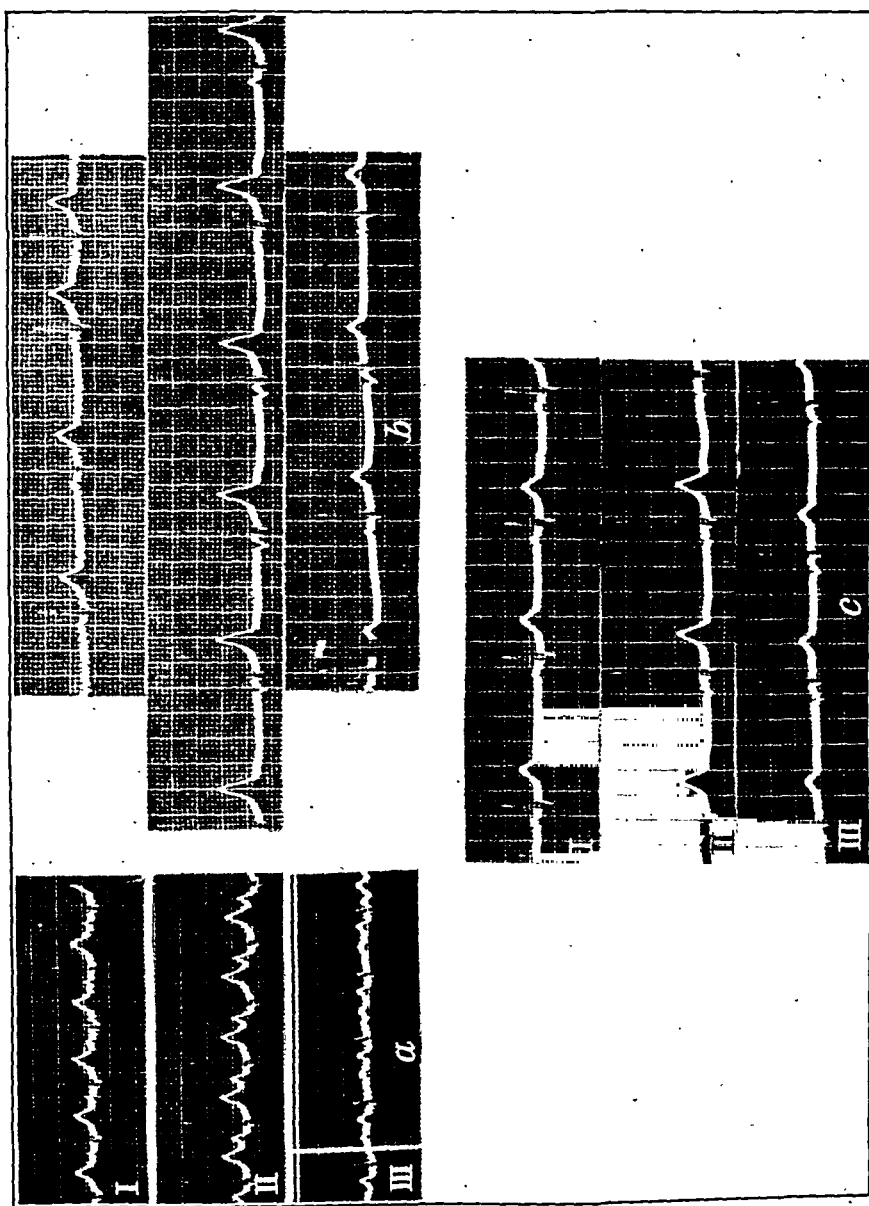


FIG. 3.—Case 36, aged 22, female, dementia precox, paranoid. (a) Control 12/6/37, 4 P.M. This patient received 145 units insulin at 7:30 A.M., 12/7/37. (b) 11:34 A.M. in coma, blood sugar 30 mg. %. Note slow ventricular rate, 50 per minute, and shifting pacemaker. (c) Patient in coma. Note slow rate and inverted P2 and 3, probably due to shifting of pacemaker in sino-auricular node.

The above factors give us some indication of how the heart may be affected by this treatment. It should be remembered that the changes are but one of the manifestations of the severe strain borne by the heart during hypoglycemic coma. Other complications, *e. g.*,

pulmonary edema, also have been recently recorded in the literature^{3,18} and have been observed by us. In view of the increasing popularity of this method of therapy, one should bear in mind the possibility of complications particularly involving the cardiovascular system.

Conclusions. 1. The electrocardiographic alterations during 58 shock treatments on 40 different patients during the hypoglycemic shock treatment of schizophrenia have been recorded.

2. Noteworthy electrocardiographic changes were obtained in two-thirds of the shock treatments. These consisted of depression of the *ST* segments, diminution of the height of the *T* wave, prolongation of the *QT* interval, auricular fibrillation, auricular extrasystoles, shifting pacemaker, sinus arrhythmia and sino-auricular heart-block.

3. The profound changes in the organism during hypoglycemic shock and its relation to the electrocardiographic changes are discussed.

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FECAL IMPACTION.

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FECAL impaction is a common cause of symptoms resembling those of rectal and intestinal disease. The subject has received all too little attention in medical literature. The condition occurs following the use of barium for roentgenologic examination of the

gastro-intestinal tract, in cases of psychosis and not infrequently among multiparous women with relaxed perineal structures. It may also occur in the loop of bowel below the site of a double-barreled colostomy that has been performed for some obstructive lesion of the lower part of the intestine. Roughage, such as bran, psyllium seed, or unusually rough food eaten in time of need or on some other unusual occasion, often causes impaction.

The symptoms of fecal impaction are variable. A common one is the frequent passage of small liquid stools associated with great difficulty of control, a condition compared to urinary retention with overflow, by Cruveilhier.^{3,4} This has not infrequently suggested "colitis" to a physician and in some cases the patients have been treated for colitis before a careful examination was made. The hard mass may produce bleeding. A non-productive urge to defecate is frequent. Enemas are often non-effectual. Constipation may alternate with apparent diarrhea. Gant⁵ listed the following symptoms as associated with this condition: "nervousness, despondency, restlessness, muddy complexion, bad breath, indigestion, barking cough, morning vomiting, cold feet, night sweats, thirst, anorexia, dizziness, albuminuria, seminal emission, frequent micturition, sphincter spasms, depression, introversion, temporary mania, sense of weight and fullness, bearing down pains." All these symptoms are undoubtedly possible but unusual and only some of them will occur in any given case of fecal impaction. The diagnosis is usually dependent on one simple examination, that is, digital examination of the rectum.

Fecal impactions in the ampulla of the rectum are easily diagnosed by this examination. Those higher in the colon often can be felt through the abdominal wall. Their peculiar doughy feel, by palpation through the abdominal wall, is characteristic. Occasionally a hard mass will slide up the bowel lumen and elude the examining finger. Diagnostic errors are at times difficult to explain. A case reported by Buzzell^{2,6} illustrates this. In this case the mass was thought to be a fetal head; involuntary micturition caused by pressure was mistaken for bursting of "the bag of waters."

The correct treatment cannot be overemphasized. It is usually simple. If possible, the mass may be broken up by digital manipulation at the time of the original examination. Hydrogen peroxide instilled into the rectum will help soften hard masses. It should be used diluted with water. Injection should be begun with a 1% solution. This may be increased to a 1.5% solution. Retention enemas of warm oil are useful and soothing and the peroxide enema should always be followed by an enema of oil that is left in the rectum as a retention enema. Small impactions may be softened with oil alone. After the impaction is removed, a regular bowel habit should be established. In Bushe's¹ publication in 1837, the following instruments were recommended for breaking up impactions: "blunt hooks, lever, gimlet, cutting forceps, narrow saw, lithotomy

forceps, a hammer and chisel, but above all, an intelligent boy with a small, well oiled hand."

The following cases are reported because they present some unusual features and because they came to our service in St. Mary's Hospital at the same time.

Case Reports. CASE 1.—A girl, aged 4, first came to The Mayo Clinic in July, 1927. She had been thrown against the foot pedals of an automobile and had sustained a severe perineal laceration. The laceration had been sutured by the family physician. She had been admitted to St. Mary's Hospital and treated for shock. In January, 1928, she returned complaining of fecal incontinence, which had been present since the accident and which had been associated with periodic constipation. At the time of her first admission in July, 1927, it had been impossible to recognize the anal sphincters. A plastic repair was attempted in January, 1928. She returned again in January, 1929, still complaining of fecal incontinence. A repair was again attempted but the extensive scarring made a good result doubtful. Thereafter her condition was rather satisfactory; she was able to predict bowel movements and had some control of defecation.

In the summer of 1937 she had further trouble, both in control and in obtaining a normal movement. Mineral oil seeped through without results. By the spring of 1938 enemas had become ineffectual. A mass was noted in the left lower quadrant of the abdomen. She noticed heaviness and discomfort in the lower part of the abdomen. Bowel movements became liquid and unpredictable; she was forced to wear diapers constantly. Blood was noticed in the stool at intervals. Her appetite became poor; her weight dropped from 100 pounds (45.4 kg.) to 89 pounds (40.4 kg.).

When she was admitted to the hospital in August, 1937, physical examination revealed a thin pale child with an anxious expression. There was a doughy movable mass in the left side of the abdomen, which extended from the iliac fossa to the level of the umbilicus. The perineal body was paper thin. A mass of feces, continuous with the abdominal mass, projected from the anal orifice. The usual laboratory examinations did not reveal anything abnormal.

The patient received the so-called residue-free diet. During a period of 3 days the impaction was broken up by periodic, manual and digital manipulation; each manipulation was followed by the use of solution of hydrogen peroxide and saline enemas. The rectum and the large intestine were completely emptied. The abdominal mass disappeared. Her appetite and sense of well-being returned. A plastic repair of the anal sphincter was done.

When the patient returned for check-up 3 months after the operation, she was feeling very well and had practically normal control of defecation.

CASE 2.—A man, aged 31, who was a lawyer, came to the clinic in July, 1938. He had been troubled with constipation since childhood. His abdomen had always been prominent. Since the age of 15 he had taken daily enemas.

In 1932 he had noticed a mass in the left side of the abdomen. Since that time it slowly but steadily had increased in size and he had been troubled with flatulence, bloating and heartburn. At different times the mass had been variously diagnosed as an enlarged spleen, a retroperitoneal cyst and other types of tumor.

Physical examination disclosed good general nutrition. There was considerable flaring of the lower ribs. The abdomen was protuberant. In the left side of the abdomen there was a round mass, which was 15 cm. in diameter and freely movable. The mass could be dented on pressure through the abdominal wall (Fig. 1). Rectal examination and the usual laboratory examinations did not reveal any abnormality. Roentgenographic examination

of the abdomen demonstrated a large mass of what was taken to be a fecalith in the left upper quadrant.



FIG. 1.—Segment of megacolon with part of the fecalith in place.

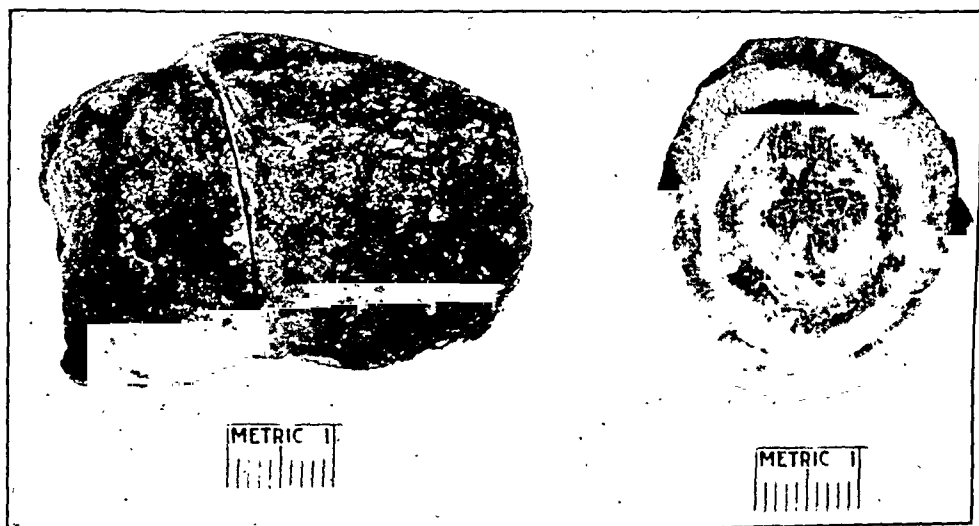


FIG. 2.—Huge laminated gall stone, the basis of impaction in the descending colon.

The patient was given a so-called residue-free diet. Treatment with solution of hydrogen peroxide and saline irrigations was begun. Eserine salicylate was given after the enemas. On several occasions pitressin was given. This procedure was repeated twice daily for 5 days. The mass was reduced to a tenth of its original size. A resection of a portion of the colon, by

exteriorization by the clamp method, was done for a localized megacolon which contained a small hard fecalith. The patient's convalescence was satisfactory.

CASE 3.—A white woman, aged 69, came to the clinic in June, 1938. For many years she had been troubled with mild indigestion after eating fatty foods. In 1934 she had had a severe attack of pain in the right upper quadrant of the abdomen which had been accompanied by vomiting. There had not been any jaundice. Since that time the pain in the right side of the abdomen had recurred at intervals.

From January, 1938 to June, 1938, she had noticed intermittent constipation and soreness in the left lower quadrant of the abdomen. On June 26, 1938, complete intestinal obstruction had occurred after barium had been given by mouth. She came to the clinic June 30, 1938, in this condition. The obstruction was largely relieved by medical measures of decompression including enemas, residue-free diet, hot abdominal stupes, parenteral fluids, and duodenal lavage.

At operation a segment of descending colon, which was the site of marked inflammatory changes that were associated with obstruction, was removed by exteriorization and resection with the three-bladed clamp. A large mass of omentum was found fixed in the region of the gall-bladder. Three weeks later she was sent home for convalescence.

Ten weeks after the primary operation she returned for closure of the colonic stoma. For several weeks she had had a sense of fullness in the rectum but had passed only mucus or blood. Enemas had been ineffectual. Examination disclosed a very firm fecal impaction which was about the size of a grapefruit. Usual measures of removal were largely ineffectual, although the mass was reduced somewhat in size. Under intravenous anesthesia a hard cylindrical mass 2.5 by 10 cm. was extracted manually.

Barium was suspected as the cause of this fecalith but incision and chemical analysis showed that it was formed about a large cholesterol gall stone (Fig. 2).

Comment. Fecal impaction has received too little consideration. It may be the cause of intense suffering. The diagnosis is usually not difficult and the treatment is exceedingly satisfactory. Relieving the symptoms produced by a huge rectal impaction makes the patient very grateful. When the impaction has been present for some time and when its constituents are very hard, digital removal may be followed by local abrasion and some discomfort. The solution of hydrogen peroxide must be carefully employed. If it is too strong, a secondary proctitis may be produced and the treatment of this condition may require many days. The whole substance of the treatment consists in breaking up the impactions as gently as possible and handling the rectum afterward in the most gentle manner possible. Thus, the use of instillations of warm oil and soothing suppositories is of as much importance as the actual dislodging of the impaction.

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ON THE ORIGIN OF AMMONIA IN THE URINE
UNDER NORMAL CIRCUMSTANCES
AND IN KIDNEY DISEASE.

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THE ammonia which is found in the urine has been shown by Benedict and Nash^{1a} to be produced in the kidney itself. For this reason the urinary ammonia cannot be considered to be an excretory product. It must rather be regarded as a metabolite of the kidney. It is because of the production and elimination of ammonia, as well as on account of the ability of the kidney to produce a urine with a hydrogen-ion concentration varying from that of the blood, that the kidney is a main factor in the maintenance of the acid-base equilibrium.

Three possibilities have hitherto been investigated as to the source of the urinary ammonia. The first of these has been considered to be urea.^{1b} The most convincing contribution pointing in this direction was made by Mann and Bollman.⁴ Working with hepatectomized dogs, they found a progressive decrease in the urea of the blood and the urine. When the urea output became very low, the urinary ammonia diminished. Intravenous injection of urea at this stage caused a definite increase in the urinary ammonia.

The second, according to Krebs,³ who worked with the Warburg method, is that ammonia is produced from amino acids. As urea formation takes place, not in the simple manner assumed by the older biochemists, but rather in a very complicated fashion, through the mediation of ornithine and related compounds, one is inclined to believe that ammonia may be produced by a reversal of this same process.

In the third place, Embden and his co-workers² have considered the formation of ammonia from adenosine-phosphoric acid as very probable. Since the excretory function of the kidney is a reversible colloidal process, similar or analogous in character to that of muscular contraction, the formation of ammonia in the kidney may occur by a process resembling this part of muscular chemistry.

In the present state of our knowledge, we can consider only the first two processes resulting in the formation of urinary ammonia; that from amino acids, and that from urea.

This work was done in an effort to determine the presence of these factors in individuals with renal diseases of various types and to see how, if at all, they differ from the normal.

Procedure. All individuals studied were in the hospital. The diet was fixed at a constant protein level (about $\frac{2}{3}$ gm. per kg. of body weight) and

fats and carbohydrates varied according to the individual's total caloric requirements. No medication was administered at any time during the study. The 24-hour urine specimens were preserved with toluene and kept on ice until examined.

In each individual the period of observation was 12 days; the first 4 were used as control, the next 4 for the administration of urea (15 gm. 3 times a day in fruit juice after meals), and the next 4 again for control.

The following determinations were made on each 24-hour specimen of urine: 1, volume; 2, specific gravity; 3, total nitrogen; 4, urea nitrogen; 5, ammonia nitrogen.

The total nitrogen was determined by the Kjeldahl method; the urea and ammonia nitrogen in some cases by urease and titration, in others by the permutit method.

A total of 24 individuals with advanced renal disease were studied in this fashion. All had evidence of marked functional impairment. A number of individuals with apparently normal kidneys were also studied.

The following 5 cases have been selected out of these to illustrate the principles involved and the type of material studied.

CASE 1.—B. B. Control. Rheumatic Heart Disease. Mitral Stenosis and Insufficiency. Blood Urea N 15.6.

1936.	Volume.	Sp. gr.	Total N.	Urea N.	NH ₃ N.	Chlorides.	Total base.	Diet: Cal. 1500; CHO 200, P 40, F 70.
3/14-15	260	1.027	3.77	3.27	0.43	1.19	27.1	
3/15-16	330	1.024	4.19	3.70	0.29	2.15	39.0	
3/16-17	240	1.028	3.87	2.49	0.47	1.90	23.2	
3/17-18	360	1.028	4.28	3.62	0.33	2.42	22.9	
3/18-19	860	1.022	16.77	15.40	0.77	3.53	77.4	Urea 45 gm.
3/19-20	1,020	1.020	21.32	19.93	0.61	2.45	54.8	" "
3/20-21	1,060	1.020	20.35	18.56	0.49	2.23	45.8	" "
3/21-22	1,090	1.026	23.76	20.05	0.83	1.85	44.9	" "
3/22-23	480	1.022	11.38	7.78	0.39	0.79	24.9	
3/24-25	310	1.020	4.65	3.59	0.52	1.48	47.4	
3/25-26	350	1.028	5.71	4.15	0.39	1.75	57.2	
3/26-27	310	1.026	4.40	3.14	0.59	1.40	50.8	

Comments: Control with no evidence of renal disease. Urinary ammonia doubled after administration of urea. Note the marked increase in output of urea when it was administered.

CASE 17.—M. S. Chronic Glomerulonephritis—Nephrotic State, Edema.

3/18/37: Blood Cholesterol 829; Protein 4.1; Alb. 1.6, Glob. 2.5.

1937.	Volume.	Sp. gr.	Total N.	Urea N.	NH ₃ N.	Diet: Cal. 2060; CHO 300; F 60.
7/23-24	750	1.018	6.90	3.90	0.68	
7/24-25	790	1.017	7.05	3.86	0.77	
7/25-26	1,130	1.014	8.16	4.84	0.80	
7/26-27	745	1.018	5.81	3.43	0.78	
7/27-28	1,690	1.013	15.55	10.41	0.98	Urea 45 gm.
7/28-29	1,570	1.013	17.00	14.32	0.91	" "
7/29-30	3,020	1.014	32.07	24.96	0.80	" "
7/30-31	3,000	1.014	28.38	24.15	1.05	" "
7/31-8/1	1,750	1.013	18.22	16.91	0.63	
8/1-2	720	1.015	7.19	4.20	0.43	
8/2-3	1,350	1.016	11.87	8.94	1.00	
8/3-4	1,270	1.016	11.99	9.94	0.37	

Comments: This patient shows a normal response in his ammonia output; it is fairly high, and increased after urea. Output of urea is delayed.

CASE 14.—R. I. Adm. 12/29/36. Chronic Glomerulonephritis, Asthenic, Anemic.
 Urine: R.B.C. plus Albumin. 1/6/37: Urea (blood) 75.9.
 2/10/37: Urea (blood) 64.9.

1937.	Volume.	Sp. gr.	Total N.	Urea N.	NH ₃ N.	Diet: Cal. 1500; P. 50; CHO 230; F 30.
2/23-24	1,730	1.013	7.02	4.65	0.33	
2/24-25	2,920	1.008	9.46	7.45	0.20	
2/26-27	Specimen lost
2/27-28	1,820	1.012	9.34	7.12	0.40	Urea 45 gm.
2/28-3/1	2,540	1.011	12.14	9.70	0.31	" "
3/1-2	2,910	1.010	12.60	9.34	0.35	" "
3/2-3	3,340	1.009	15.83	12.99	0.30	" "
3/3-4	3,000	1.010	12.93	10.71	0.21	
3/4-5	1,800	1.011	8.87	7.22	0.29	

Comments: The urinary ammonia is fairly high, but is unaffected by the administration of urea. The diuresis is only moderate and the excess urea is eliminated very slowly.

CASE 5.—R. M., 21. Chronic Glomerulonephritis, Nephrotic Syndrome, Left Pleural Effusion. 9/14/35: Blood Urea N 21.6. 9/27/35: Blood Urea N 16.0.

1935.	Volume.	Sp. gr.	Total N.	Urea N.	NH ₃ N.	Diet: Cal. 1500; P 45; CHO 200; F 60.
9/16-17	480	1.020	4.64	2.54	0.09	
9/17-18	340	1.024	4.76	2.25	0.08	
9/18-19	580	1.020	5.10	3.95	0.08	
9/19-20	640	1.017	6.77	3.81	0.06	
9/20-21	1,480	1.015	13.99	11.90	0.12	Urea 45 gm.
9/21-22	1,130	1.017	17.49	9.68	0.51	" "
9/22-23	1,800	1.014	19.69	16.78	1.06	" "
9/23-24	1,150	1.012	18.10	10.83	0.05	" "
9/24-25	610	1.014	8.80	5.85	0.03	
9/25-26	810	1.015	13.92	5.00	0.04	
9/26-27	980	1.015	12.81	6.28	0.03	
9/27-28	750	1.014	7.52	5.00	0.04	

Comments: This patient was apparently unable to produce urinary ammonia on a limited nitrogenous intake, but the administration of urea produced a considerable increase in the excretion of NH₃, which, however, became rapidly exhausted. A good diuresis was produced at the same time, and the urea output increased considerably. If we remember that there was about 80 gm. of nitrogen additional in the urea administered, we can see that only about one-half was excreted during the 4-day period and that urea was increased in the urine for days beyond that.

CASE 3.—I. D. Acute Hemorrhagic Glomerulonephritis; Uremia; Thrombocytopenic Purpura; Multiple Hemorrhages Throughout Body; Coronary Thrombosis; Gastric Ulcer; Cholelithiasis. Blood Urea N: 7/19/35, 59.7; 7/31/35, 37.3; 8/12/35, 39.3; 8/28/35, 91.8.

1935.	Volume.	Sp. gr.	Total N.	Urea N.	NH ₃ N.	Diet: 1500 Cal.; P. 30.
7/30-31	940	1.014	8.55	4.94	0.06	
7/31-8/1	820	1.014	8.14	5.09	0.10	
8/1-2	1,080	1.014	8.65	5.65	0.07	
8/2-3	830	1.014	8.30	5.35	0.08	
8/3-4	1,630	1.014	14.52	9.93	0.11	Urea 45 gm.
8/4-5	1,780	1.012	17.52	14.08	0.07	" "
8/5-6	1,620	1.012	18.05	13.18	0.06	" "
8/6-7	1,600	1.013	15.86	13.22	0.05	" "
8/7-8	1,800	1.008	14.92	13.47	0.04	
8/8-9	1,330	1.012	16.08	8.37	0.05	
8/9-10	1,200	1.012	11.62	6.67	0.04	
8/10-11	920	1.010	9.38	4.30	0.03	

Comments: The administration of urea caused a mild diuresis with increased urea excretion, but by no means sufficient to determine the increased intake. Urinary ammonia remained persistently low during the entire period of observation. This individual showed advanced renal disease with very slight ability to form ammonia from either the diet or administered urea.

Comment. The amount of ammonia excreted in the urine depends upon a number of factors. First, there is the amount of strong acid produced in the intermediary metabolism or introduced into the system. Second, it depends upon the ability of the organism to form ammonia from its parent substances. Furthermore, there must be considered ammonia salts administered for experimental or for therapeutic purposes.

Normally, strong acids are preferably produced from proteins. Sulphuric acid, the strongest, arises from the oxidation of the sulphur derived from proteins. Its excretion through the kidneys invariably requires an equivalent amount of base, thus endangering the stock of alkali of the blood and tissues.

Phosphoric acid, though not as strong as sulphuric, usually exceeds it in quantity. It originates from various phosphoric esters, and is excreted both as an acid salt and as a basic salt, the latter carrying away twice as much base as the former.

Weak acids are excreted totally or partly as such, depending on their degree of dissociation, thus sparing base.

The production of ammonia, and of ammonia salts, prevents the loss of valuable fixed alkali. Under normal circumstances, therefore, the level of ammonia in the urine is commensurate with that of the protein metabolism, and is parallel to the oxidation of sulphur, that is, the formation of sulphuric acid.

Nevertheless, if the presence of ammonia in the urine were due exclusively to the task of maintaining the acid-base equilibrium, it should be missing in alkaline urine. Alkaline urine occurs under a variety of circumstances. It is produced by an intake of alkali in excess of the intermediary acid formation. It occurs in order to compensate for loss of acid in the gastric juice during the period of secretory activity of the stomach. Finally, in "pure" phosphaturia or alkalinuria, we find alkalinity of the urine without any of the above factors, due to some disorder of the autonomic nervous system, and probably to the temporary inability of the kidney to produce an acid urine. In such instances, in spite of the alkaline reaction, the kidney continues to produce ammonia, sometimes on a larger scale than normal. Apparently, therefore, a fraction of the urinary ammonia is formed, regardless of the renal mechanism responsible for the maintenance of the acid-base equilibrium.

Ammonia, though a base, and though of great importance in the formation of amino acids and in the chemistry of muscular contraction, is physiologically absolutely different from the fixed bases. It is present, if at all, in the blood and in the tissues in exceedingly small quantities, and thus it plays no direct rôle in the acid-base equilibrium. The small figure for milligrams per cent of ammonia obtained in the chemical analysis of the blood does not rise in the acidosis produced by the introduction or by the increased formation of acids. Of course, it is well known that ammonia is continuously

produced on a large scale from the amino acids, but it disappears at the same rate.

In normal individuals the urea output in the urine will vary considerably. Under certain circumstances, chiefly when the intake of nitrogen is limited, this output may be considerably reduced (B. B., Case 1). It is to be noted, however, that the urinary ammonia ranged well above 0.30 gm. of nitrogen per day, and that with the administration of urea the output of ammonia rose considerably.

With severe renal damage, this mechanism was found to be altered.

Results in Kidney Disease.—*Group I.* Some (M. S., Case 17) showed essentially a normal response. The ammonia output was good and it was increased by the oral administration of urea. It is interesting to note that the cases falling into this group differed clinically. One was an individual with polycystic kidneys and only slight urea retention in the blood (25 mg. %). Another was a boy with glomerulonephritis and a blood urea nitrogen of 80, apparently much more serious impairment of renal function. The case illustrated was a young man of 27 with a nephrotic picture (blood cholesterol 829; albumin 1.6; globulin 2.5; urea 18.1). These patients usually showed considerable delay in the excretion of ingested urea.

Group II. Others showed an output of ammonia corresponding to the nitrogenous intake, but the ingestion of urea in fairly large doses was followed by either a temporary, rapidly exhausted increase in the excretion of ammonia (R. I., Case 14) or no increase at all.

Group III. Other patients were apparently unable to produce urinary ammonia in an amount corresponding to the nitrogen intake, but could form ammonia when urea was administered (R. M., Case 5).

Group IV. Still others showed persistently only small traces of ammonia in the urine, not increased by the intake of urea (I. D., Case 3).

The diuretic effect of the urea certainly did not depend on the formation of ammonia, because there could be shown no relation between the diuresis and the excretion of urea on one hand, and the excretion of ammonia on the other.

In kidney disease there were all combinations of impairment and non-impairment of the two mechanisms of ammonia formation.

The following table summarized our 24 cases of renal disease:

Group I.	A+ U+*	6 cases
Group II.	A+ U—	9 cases
Group III.	A— U+.	4 cases
Group IV.	A— U—	5 cases
		<u>24 cases</u>

* + = present. — = absent. A = formation basically from amino acids
U = formation from urea.

These observations seem to point to the fact that ammonia formation from urea represents a particular index of kidney function, while the formation of ammonia from other precursors, is another.

The fact that some of these individuals (notably F. B., Case 13, not illustrated) possessed good ammonia formation in the kidney in spite of a very high blood urea, merely indicates that the various impairments of renal function, though frequently parallel, are not necessarily so; so that some kidneys, though unable to excrete sufficient urea, can still produce ammonia.

If the kidneys are functioning properly, increased output of ammonia results in the sparing of the base. If this cannot occur, the absence of ammonia formation tends to lead to a wasting of fixed base, a diminution of alkali reserve and sooner or later, acidosis.

Summary and Conclusions. Studies were made on individuals with normal kidneys and on those with renal disease in an attempt to clarify the mechanisms by which ammonia is produced in the urine and the rôle it plays in the maintenance of the alkali reserve.

On 24 individuals kept on constant nitrogenous intake, the urinary nitrogen output was studied before and after the administration of urea. Five of these cases were selected as illustrations.

It was found that there are at least two ways in which ammonia is produced in the urine, from urea, and from other precursors (most likely amino acids); and that these two mechanisms are not necessarily related; that ammonia formation from urea represents one index of renal function and that formation from amino acids represents another. Normally, this all occurs in the kidney.

Individuals with renal disease do not necessarily lose these two powers at the same rate; one mechanism may be preserved when the other has been lost. A certain margin of safety thus tends to be maintained, and the ability to produce some ammonia and thus spare some fixed base is retained for a long time.

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CHROMIUM POISONING IN INFANCY.

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A SURVEY of the literature shows that not much is known definitely about the systemic effects of poisoning by chromium. The soluble salts of chromium are irritants to skin and mucous membranes

to such an extent that not much systemic absorption is liable to occur. In those cases in which absorption has occurred, as shown by the presence of chromium in excretions, the symptoms have suggested that the effect was chiefly upon the nervous system although, so far as we can discover, no neuropathologic studies have been made in such cases. We have had the opportunity to study, clinically, a case of chromium poisoning in an infant which presents features of great importance not only to physicians but also to toxicologists.

Case Report. The patient was a female, aged 14 months, the only child of healthy parents, and with no history of epilepsy on either side. She was delivered by Cesarean section and aside from a moderate feeding difficulty at first, she had been in good health. Her mental development was normal.

On August 28, 1938, she seemed rather dull and inactive, and appeared to have a slight fever. At 4 A.M. of August 29, she had her first convulsion, which was generalized. Following this she remained in a stupor and began having a series of convulsions at irregular intervals, which sometimes involved the right side of the body, sometimes the left, and at other times only one part, such as one side of the face or a leg.

She was seen by one of us at that time (J. F. S.) who found the rectal temperature 103° . There was no rigidity of the neck. The pupils were dilated but reacted to light. The ears were negative but the throat appeared to be inflamed. There was a soft systolic murmur at the base of the heart. The lungs were clear, and the abdomen negative. There was no diarrhea but there was mucus in the stools. The convulsions were treated with a sedative and the patient removed to a hospital. She remained unconscious and continued to have convulsions. Repeated examinations showed no change in her condition.

On August 31, it was noted that the pupils were dilated, responded sluggishly to light, and at times there was a divergent strabismus. The ocular fundi were negative. There was no paralysis of the face, tongue, or extremities, and no disturbance in muscle tone. The tendon reflexes were normal and equal on each side. The plantar reflexes were normal. There was no Kernig's sign and no Brudzinski sign. During the course of the examination the patient had several attacks, one involved the right side of the face, and another the left leg. They lasted about a minute and the movements resembled those of Jacksonian epilepsy. Although apparently unconscious, she would occasionally cry out. A few râles were heard in the lungs but a Roentgen ray examination of the lungs was negative. There was a faint systolic murmur at the base of the heart.

The urine was straw colored, cloudy, and with acid reaction. It contained a trace of albumin but no sugar, and on September 3, 1938, no albumin but a trace of sugar. Subsequent tests up to October 3, 1938, were negative. There were no casts at any time. The first blood examination showed 3,500,000 red blood cells, 16,300 leukocytes with a hemoglobin of 70%. The neutrophils were basophilic but there was no basophilic stippling of the red blood cells. The Kahn test on the blood was negative and the blood N. P. N. was 31.9 mg. %. The blood and leukocyte counts, repeated daily, gradually returned to normal.

A spinal puncture was done Sept. 1, 1938. The cell count was not increased. Pandy's reagent gave a positive reaction but the test with ammonium sulphate was negative. The total protein was 16. The gold sol. 001100000. The Kahn test was negative.

The clinical history and findings suggested an encephalitis, either of toxic or infectious origin. A lead encephalopathy in an infant would cause somewhat similar, though not identical, symptoms. One week previous to the onset of the trouble the child was seen eating the paint from a souvenir tray. The father said that the paint had been daubed on thickly and that he had been able to remove some of the material from the patient's mouth at the time.

The urine was examined in the State Laboratory at Lansing, on Sept. 1, 1938, for lead, chromium, and mercury, but only chromium was found. This was repeated on Sept. 2, with the same result. On Sept. 12, 16, and 23, no chromium was found. The feces showed none on Sept. 1, but a trace of chromium was found in Sept. 2, and none on Sept. 19.

The chemist reported that the paint material was a silicate with the pigment an insoluble chromite ore.

The child was treated with sedatives as necessary, intravenous Ringer's solution, and was given 2 blood transfusions. Syrup of the iodide of iron was given by mouth when possible. Magnesium sulphate enemas were given daily. The temperature returned to normal on Sept. 4, and convulsive seizures stopped on the 7th day, but following this she began having choreiform movements. These subsided gradually and the patient continued to improve, although still in a semi-stupor at the end of 6 weeks. Her improvement was slow and in March, 1939, she was just beginning to creep. She could balance in sitting. She could definitely see, hear, smell, and taste. Her reflexes were normal, and the ocular fundi were normal. There was no paralysis.

A search of the literature shows that this case is important in several ways and in some respects, unique. Practically all of the cases of systemic chromium poisoning that have been reported have resulted from taking potassium bichromate, usually in solution. In some industries the inhalation of chromium dust may cause ulceration of the mucous membrane of the nose, and those who may immerse the hands in chromate solutions, photographers for instance, may develop excoriations of the skin, the so-called "chrome holes," but usually there are no systemic effects in such cases. Bichromate is a powerful irritant to the stomach so that the patient vomits and not much is absorbed although in a case reported by Jonssen where the patient drank a 5% solution of potassium bichromate, painful convulsions of the arms and legs came on after 6 hours. In the case reported by Goldman and Karotkin¹ the temperature went up to 101°. This case and the one we report, are the only cases in which chromium was recovered from the urine, but in neither one was there definite evidence of nephritis. Fever in chromium poisoning is not unusual. In our case, the temperature of 103° F. was higher than in other reported cases but the fact that it was a rectal temperature in an infant might account for this difference. The dilated pupils which was rather a striking feature in our case, is a common symptom of chromium poisoning.²

Poisoning by chromium is not common. Goldman and Karotkin could find only 69 cases in the literature. In our search we have found no other case of chromium poisoning in an infant. Nor have we been able to find a case in which the poison gave only a slow

acting systemic effect without gastro-intestinal symptoms. We believe that the chromium in this case was not absorbed into the system until the chromium-containing material had been acted upon by some substance in the gastro-intestinal tract, probably liberating the chromium gradually.

Summary. A case is reported of chromium poisoning in an infant due to the ingestion of a paint containing a relatively insoluble chromium compound. There was no evidence of local gastro-intestinal irritation. The symptoms were systemic and showed evidence of the effect on the nervous system. The most important symptoms were convulsions, stupor, dilated pupils, negative neurologic findings, and normal spinal fluid. Chromium was found in the urine and feces.

REFERENCES.

- (1.) Goldman, M., and Karotkin, R. H.: *AM. J. MED. SCI.*, 189, 401, 1935. (2.) McNally, W. D.: *Toxicology*, Chicago, Industrial Med., p. 127, 1937.

BOOK REVIEWS AND NOTICES

IMMUNITY PRINCIPLES AND APPLICATION IN MEDICINE AND PUBLIC HEALTH. An Exposition of the Biological Phenomena of Infection and Recovery of the Animal Body from Infectious Disease, with Consideration of the Application of the Principles of Immunity to Diagnosis, Treatment, and Prophylaxis and Their Usefulness in the Control of Epidemics. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunology, Harvard Medical School, JOHN F. ENDERS, Ph.D., Assistant Professor of Bacteriology and Immunology, Harvard Medical School, and LEROY D. FOTHERGILL, M.D., Assistant Professor of Bacteriology and Immunology and Associate in Pediatrics, Harvard Medical School. Pp. 801. Fifth edition of "Resistance to Infectious Diseases." New York: The Macmillan Company, 1939. Price, \$6.50.

THE aim of the present edition is clearly stated by the authors as representing an endeavor to meet the need for increased correlation between its principles as revealed in the laboratories and their application to the problems of the clinic and of public health. "The most notable advances of recent years in this subject (immunology) have resulted from intimate collaboration of the bacteriologist and the chemist on the one hand, and the bacteriologist and clinician on the other." Much of the older material has been eliminated to make room for the newer knowledge. The book is conveniently divided into two parts, *i. e.*, principles and theory, and the application of immunological knowledge to medicine and public health. Throughout, both the interdependence of theory and practice has been stressed, thus "the laboratory worker, turning to the practical sections, may derive stimulus from the recognition that many of the principles at first conceived without obvious possibility of applied value have ultimately served to enrich diagnosis, prevention or therapy; and the practitioner, referring to Section II for details of specific procedures, can turn back to the chapter on principles and there find discussions which will aid him more fully to understand the observations and reasoning upon which many of the methods used in practice are based." The reader will find that the aims of the writers have indeed been fulfilled. B. L.

AN INTRODUCTORY GUIDE TO BIOCHEMISTRY. By SIDNEY BLISS, Ph.D., Professor of Biochemistry, Tulane University School of Medicine. Pp. 103. Philadelphia, W. B. Saunders Company, 1939. Price, \$1.25.

ACCORDING to the author the purpose of this brief outline is to give to the prospective student of biologic chemistry a general idea of the subject as a whole before beginning a detailed study of the various subjects concerned. As such it might be of some practical value. However, it is difficult to see what type of student the author had in mind in selecting the material. For example, the statement is made that a base is the chemical opposite of an acid, and again unsaturation in organic compounds is explained, apparently assuming no knowledge of either inorganic or organic chemistry on the part of the student. In contrast to this, in discussing physiologic oxidation of fats, it is stated that oxidation takes place on the beta carbon atom without further explaining which carbon atom is so

labeled. Some definitions, such as that a fat is a salt of the organic base glycerol, could also be questioned.

In spite of these criticisms the author has succeeded in outlining the field of physiologic chemistry in a very few pages, and although it is not written essentially for the layman, a knowledge of neither chemistry nor physiology would be necessary to understand and enjoy this simple treatise.

J. J.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. An Introduction to the Study of Nervous Diseases. By **FREDERICK TILNEY, M.D., Ph.D.**, Director Emeritus, Neurological Institute, New York, and **HENRY ALSOP RILEY, M.D.**, Director and Attending Neurologist, West Service, Neurological Institute; Professor of Neurology and Neuroanatomy, Columbia University, College of Physicians and Surgeons, New York. Foreword by the Late **GEORGE S. HUNTINGTON, Sc.D., M.D.** Pp. 851; 600 illustrations. Third edition. New York: Paul B. Hoeber, Inc., 1938. Price, \$10.00.

This new edition of a well-known book reflects the advances of our knowledge in the field of neurology. While the basic plan of the earlier editions has been retained, many sections have been rewritten to present current views. This is especially true of the discussion of the cerebellum, the cerebral cortex, the interstitial tissue, the hypothalamic region, the hypophysis and the epiphysis. Despite the addition of much new material, the bulk of the former volumes has been reduced by judicious condensation and by the elimination of detail of interest mainly to the comparative anatomist. Like the two previous editions, the present work represents ripe scholarship and adequately fulfills the aim of the distinguished authors: to correlate form and function, and, by the extensive citation of actual cases, bridge the gap between neuroanatomy, neurophysiology and clinical neurology.

B. L.

THE MEDICAL CLINICS OF NORTH AMERICA. VOL. 23, No. 3 (NEW YORK NUMBER, MAY, 1939). Pp. 277; 30 illustrations. Philadelphia: W. B. Saunders Company, 1939.

Of the 22 articles in this number, 15 are included in the symposium on pediatrics, each on a different phase—nosology, prognosis and especially treatment. The remaining articles treat such topics as lipoidosis, pellagra, vitamin deficiencies, flaccid paraplegias and the shock treatment of psychosis. One is mildly surprised to meet Senator's antiquated term "auto-intoxication of intestinal origin," and still more so when one reads further that the diagnosis must be based, not on laboratory studies, but "largely" upon clinical impressions. Doubtless colonic irrigations will help many cases diagnosed in this way.

E. K.

HYPERTENSION AND NEPHRITIS. By **ARTHUR M. FISHBERG, M.D.**, Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 779; 40 illustrations and 1 colored plate. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$7.50.

The rapid progress in the clinical and experimental investigation of Bright's disease has necessitated a complete revision of this work. The following are but a few of the new subjects discussed, and of old sections rewritten: Goldblatt's work on hypertension, Masugi's experimental production of glomerulonephritis, the Addis count, Cushing's syndrome, nature and treatment of the toxemia of pregnancy, hemoglobinuric nephrosis;

papilledema in hypertension; mercurial diuretics, etc. Simple laboratory tests, such as can be performed by any practitioner, are fully described. It is emphasized that the more elaborate laboratory procedures are needed in only a minority of patients. The book is an excellent guide, and rightly deserves the popularity it has long enjoyed.

B. L.

LABORATORY MANUAL OF THE MASSACHUSETTS GENERAL HOSPITAL. By FRANCIS T. HUNTER, M.D. Pp. 119. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$1.75.

SINCE the second edition of this booklet more than 10 years ago, diagnostic, prophylactic and minor therapeutic procedures have been greatly modified and developed. This progress is faithfully reflected in the present edition. In some cases obsolescent procedures are retained, apparently on the principle of being sure that you are on with the new love before you are off with the old. This booklet continues to be one of the best of its kind.

E. K.

RICHTLINIEN PRAKTISCHER ORTHOPÄDIE. By DR. ALBERT LORENZ. Pp. 464; 123 illustrations. Wien: Franz Deuticke, 1939. Price, Paper, M. 15; Bound, M. 16.80.

THIS work, as the author indicates, is intended for the orthopedic specialist rather than for the medical student or general practitioner. Description of material which would be of importance to the latter is generally sketchy and most of the treatise deals with technical detail as to therapy, both operative and non-operative.

Much of this book was written while the author was in New York and admittedly he has paid a great deal of attention to the English and American literature. This work is divided into 35 chapters, dealing with plaster bandaging, physiotherapy, anesthesia, flat feet, arthritis deformans, tuberculosis of bones and joints, various congenital deformities, such as wry neck, club feet, Sprengles deformity and congenital dislocation of the hip. There are also chapters on spastic paralysis, infantile paralysis and the muscle dystrophies.

In the field of fractures mention is made only of the fracture of the neck of the femur. In this chapter in addition to presentation of the Whitman abduction and the nailing method, the author has included an operative procedure of his own, which in the Reviewer's opinion, is possibly of value in certain chosen cases.

Unfortunately, there is no mention either of bone deforming conditions such as arthritis deformans or hyperparathyroid states (osteitis fibrosa cystica) nor is any space allotted to tumors.

Of particular interest is the detailed chapter on congenital dislocation of the hip, in which much discussion is allotted to the bloodless and to the operation treatment. The author believes in relatively prolonged fixation in plaster after bloodless reduction and differs from one American authority in a very naive fashion. This latter orthopedic surgeon frankly states that his experience proves bloodless reduction a failure if it is not satisfactory after four months of immobilization in plaster. The author says, that with that opinion he disagrees, but in "rich America, time is money."

In his introduction the author goes into some detail about the question of congenital deformities and makes the statement that eradication of such deformities might well be attained by the process of voluntary sterilization. One might see eye to eye with him regarding certain hereditary conditions, but the exact logic of this applied to congenital deformities is

a bit obscure. Possibly, into medicine, too, has crept some of the new German ideology.

In general, however, the book is a good one and both of interest and value to those orthopedic surgeons who are familiar with German and, though lacking in some aspects as in fractures, though mirroring to a large degree the author's opinions. It is of good interest and value for those orthopedic surgeons who are familiar with German.

I. S.

IT'S MORE FUN TO BE THIN. By JEAN Z. OWEN. Pp. 182; illustrated. Boston: Marshall Jones Co., 1939. Price, \$2.00.

IN most books and magazine articles written with the purpose of helping those in need of advice in regard to reducing, diet and exercise are stressed and outlined in a matter of fact way, like a doctor's prescription, but the author of "It's More Fun to be Thin," has made an enjoyable game of this endurance test. In this very delightful and entertaining book, she has demonstrated, by a series of case histories, that it is much to a woman's advantage in every way to keep her figure trim. The rules of the game are well-planned diet, exercise, an interest in things other than food and, if needed, the supervision of a physician. While this book is written in a gay refreshing style, the contents are entirely accurate and reliable. This book should be welcome to doctors to recommend to their obese women patients.

M: S.

RURAL MEDICINE. Proceedings of the Conference held at Cooperstown, New York, October 7 and 8, 1938. Pp. 268; 15 illustrations, 13 tables and 35 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, \$3.50.

THIS book presents the papers read and discussed at a conference on Rural Medicine organized by the staff of the Mary Imogene Bassett Hospital of Cooperstown. The purposes of the conference were as follows:

1. To provide a forum for discussion of problems of rural medicine and to give publicity to ideas and suggestions for accelerating progress in rural hygiene.
2. To define and set apart as distinct problems those which have a special relationship to the health of rural communities.
3. To present a true picture of rural morbidity, as far as the experience of a single rural hospital may serve for this purpose.
4. To stimulate unsentimental scientific scrutiny of those conditions which influence the incidence of disease and disability in rural populations and to apply such scrutiny to the problems of rural medicine.

The conference brought together a noteworthy gathering of experts on public health, medical education, organization of medical service and rural life. It held four sessions, devoted respectively to rural morbidity, health department programs and school health programs in rural areas, postgraduate medical education in rural areas and economics of rural medicine. At these sessions, papers were presented by members of the staff of the Bassett Hospital, by local physicians, by biostatisticians who had studied the local community and by experts on the various topics discussed. The volume contains 16 papers and the excellent discussions which they evoked, and is concluded by an extensive bibliography of Rural Medicine.

This collection of papers raises many questions regarding Rural Medicine and answers conclusively but a few of them. It demonstrates clearly, however, that plans for the improvement of medical service must be adaptable to local needs and must have sufficient flexibility to meet many variations in local conditions and attitudes in order to be effective. The problems of rural medicine are set forth from a variety of aspects, and those interested

in the changing conditions of medical care should study this excellent approach to the subject which this book represents, namely an effort to study at first hand and at close range one phase of the problem of medical service by a distinguished group of leaders in public health and medical service.

The discussion of economics of rural medicine is noteworthy. Beginning with accounts of experience in this field, the discussion is continued by close observations and sensible interpretations of the local situation followed by a broad general discussion both from a liberal and from a more conservative point of view.

The conference reported in this book is an excellent example of the educational process which is essential, if intelligent coöperation is to be effected between the public and the medical profession, in working out the details of any program of medical service which may be advanced by legislation. Dr. George Mackenzie and his colleagues of the Mary Imogene Bassett Hospital deserve much credit for inaugurating such a valuable method of stimulating sound thinking based on facts, which is especially valuable at this time of controversy regarding medical service. G. R.

A TEXTBOOK OF ORTHOPAEDIC NURSING. By EVELYN C. PEARCE, Sister Tutor, The Middlesex Hospital. Foreword by the Late SIR ROBERT JONES, Bart., K.B.E., C.B., F.R.C.S., and an Introductory Chapter by DAME AGNES HUNT, D.B.E., R.R.C., Founder and Honorary Superintendent, the Shropshire Orthopaedic Hospital and Agnes Hunt Surgical Home, Oswestry. Pp. 230; 101 illustrations. Second Edition. London: Faber & Faber Ltd., 1939. Price, 7s. 6d.

THE object of this book, the first textbook on Orthopaedic Nursing ever written, according to the author is "to help nurses in training in the general hospitals of the country to a better understanding of the treatment of orthopaedic cases and consequently to a deeper interest in this branch of surgical nursing." In the Introductory chapter written by Dame Agnes Hunt, founder of the Shropshire Orthopaedic Hospital and Agnes Hunt Surgical Home, the object of Orthopaedic work is stated as being that of Prevention, Treatment and Training. The importance of the nurse as a teacher in preventive measures is illustrated graphically by this nurse, who has had so much experience in this particular clinical field. Some points on the Anatomy of those structures involved in deformity and disease are described in the first chapter and then on to congenital deformities for which treatments are described clearly in the text and by photographs, drawings and Roentgen-ray photographs. The infectious diseases that so often result in deformities, such as acute anterior poliomyelitis, spastic paralysis (Little's disease), rickets and inflammatory disease of bone, including tuberculous arthritis, osteoarthritis, spondylitis and fibromyositis, have a chapter devoted to each, in which the disease is described as to etiology, common deformities occurring (with pictures showing typical conditions) and the treatment and nursing care. There is a chapter on deformities of the vertebral column with many illustrations showing every type occurring commonly and also positions assumed in exercises used to overcome these conditions. A chapter on injuries to bone and joint, fractures and dislocations and internal derangements of the knee joint describes many kinds of each of these conditions with treatments. The last chapter covers applications of splints and extensions, preparation of the skin before operations and application of plaster of Paris. Here not only by rules but by many photographs and drawings is shown the art of carrying out these procedures. This book should be in the library of every school of nursing as it contains so much material of interest to nurses in orthopaedic work and to those who include this clinical field in their general field of nursing. M. S.

THE PATIENT AS A PERSON. A Study of the Social Aspects of Illness. By G. CANBY ROBINSON, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. Pp. 423. New York: The Commonwealth Fund, 1939. Price, \$3.00.

WE have passed through a generation in which Chairs of Medicine were held by persons especially trained in pathology. This led to great interest in that kind of disease which could be demonstrated at necropsy, and a corresponding lack of interest in "functional" diseases. There has doubtless always been some protest against this trend. Medical Philadelphia still tells stories of patients whom Osler passed by with a wink, who went to Weir Mitchell and were cured. Later Peabody's book, "Doctor and Patient," attracted attention. Now comes Dr. Robinson with much documented evidence. He took 174 unselected patients admitted to the Johns Hopkins Hospital, gave them long interviews at the hospital, and followed them to their homes. He promptly discovered many important facts about which the hospital doctors were entirely ignorant, *e. g.*, in 66% adverse social conditions bore a definite relation to their illness. A common error on the part of the hospital doctor was that the patient's emotional disturbances were not given adequate consideration. Under such circumstances the time and money wasted in useless laboratory work and irrelevant studies must have reached no small total.

Dr. Robinson suggests a solution to these problems. He would have departments covering the social aspects of illness established in our scheme of medical education. Meanwhile, each third year student is assigned one out-patient to study, under supervision, as a total individual. After this study is complete the data are presented in a conference attended by public health administrators, medical social workers, psychiatrists, and so on.

Surely everyone familiar with the deficiencies of hospital practice will applaud the author's efforts to improve the handling of the large group of hospital patients incapacitated, in whole or in part, by the social maladjustments of our era.

I. S.

STUDIES ON THE CHANGING INCIDENCE OF PEPTIC ULCER of the Stomach and Duodenum. By GUNNAR ALSTED, M.D., Privat-docent at the University of Copenhagen; Assistant Physician and Member of the Staff, Bispebjerg Hospital, Copenhagen. With a Preface by PROFESSOR E. MEULENGRACHT. Pp. 148; 12 illustrations. Copenhagen: Ejnar Munksgaard, 1939. Price, 10/-.

ALSTED believes that the incidence of peptic ulcer in the female sex has decreased during the past half century, while it has remained unchanged in the male. In the male, however, its location has shifted from the stomach to the duodenum and it has become more chronic. Its chronicity in men has led to a greater number of male hospital admissions for ulcer, and this together with the actually decreased incidence in women accounts for the altered sex relationship. His conclusions are based on an exhaustive analysis of statistical data, which some may feel are too limited; but certainly his arguments seem sound and they deserve further consideration. The book should be read by all interested in the subject.

T. M.

ROENTGEN TECHNIQUE. By CLYDE MCNEILL, M.D., Louisville, Kentucky. Pp. 315; 268 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.00.

THE author's endeavor to reduce the contents of a large volume to a useful and practical reference book has been successful. The book is divided

into four parts: head, extremities, trunk and exposure technique. The standard Roentgen positions are dealt with in a systematic manner, each position being accorded 2 full pages. Photographic illustrations showing the tube, patient and cassette appear on the left hand page while descriptive matter and technical factors appear on the right. The book is designed primarily for average equipment, and with this in mind, methods of pineal localization, interpedicular measurements and pelvimetry are included. Such recent advances as kymography and tomography are briefly described, and in places where the subject matter is inadequate, references have been added. The purpose of the book seems to be to bring the essential facts of technique together in a compact, handy manner. The author has eliminated the verbiage of the subject which he treats and held to generally accepted procedures. This book is recommended as a handbook to those interested in the basic facts of Roentgen technique. E. G.

MEDICAL VOCABULARY AND PHRASES. English, German, French, Italian, Spanish. By JOSEPH S. F. MARIE. Foreword by CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-Esophagology and Consultant in Broncho-Esophagologic Research, Temple University, School of Medicine, Philadelphia. Pp. 358. Philadelphia: P. Blakiston's Son & Co. Inc., 1939. Price, \$3.00.

THE German, French, Italian and Spanish equivalents of some 7000 English medical terms, arranged in parallel columns for easy comparison. Also 9 pages of phrases prepared for use in conversation with nurses or patients. The potential value of such a book is obvious, and could well justify Dr. Jackson's enthusiastic foreword: "All my medical life I have wanted just such a book as this. It makes me sad to think of the thousands of weary hours it would have saved me, hours spent in handling a clumsy stack of dictionaries." Unfortunately, the value of the book is decidedly impaired by the large numbers of mistakes, nearly all of them in the German terms. A casual inspection of the first hundred pages disclosed 112 errors (more than 1 for every 25 English words): errors that are mostly the evidence of both unintelligent and careless proofreading, as when the word *clavicle* is variously translated in three places as "die Schlüsselbein," "das Schlüsselbein," and "das Schlüsselbein." It is to be hoped that an early revision will produce what could be an excellent book. R. K.

FEVER THERAPY TECHNIQUE. By JACK R. EWALT, M.D., Resident Psychiatrist, Colorado Psychopathic Hospital; Instructor in Psychiatry, University of Colorado School of Medicine, Denver; ERNEST H. PARSONS, M.D., Captain, Medical Corps., United States Army; Neuropsychiatrist, Sternberg General Hospital, Manila, Philippine Islands; STAFFORD L. WARREN, M.D., Associate Professor of Medicine in Charge of Division of Radiology, University of Rochester School of Medicine, Rochester, N. Y., and STAFFORD L. OSBORNE, B.P.E., M.S., Associate in Physical Therapy, Northwestern University School of Medicine, Chicago. Foreword by FRANKLIN G. EBAUGH, M.D. Pp. 161; 16 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.50.

A CONCISE accurate presentation of the various methods used to induce therapeutic fever. The authors have been particularly interested in mechanical devices, including the radiant energy cabinet, the hypertherm, and high frequency currents, so that the descriptions of these techniques are excellent. (One might differ, however, with their views as to some of the principles

underlying fever therapy and consequently their evaluation of non-specific protein shock treatment.) The book is considered by the authors as an adjunct to, not a substitute for, the post graduate instruction which they feel is necessary for the physician who wishes to administer fever therapy by any of the mechanical methods.

R. K.

STUDIES FROM THE CENTER FOR RESEARCH IN CHILD HEALTH AND DEVELOPMENT, SCHOOL OF PUBLIC HEALTH, HARVARD UNIVERSITY. (Monograph of the Society for Research in Child Development, Vol. IV, No. 1, Serial No. 20.) I. The Center, the Group under Observation, Sources of Information and Studies in Progress. By HAROLD C. STUART, M.D., and STAFF. Pp. 261; 66 illustrations. Washington, D. C.: Society for Research in Child Development National Research Council, 1939. Price, \$1.75.

DR. STUART has presented a preliminary report of a very extensive investigation of child development which was begun in 1930. He describes the growth of the Center and gives details of the methods used and the conditions under which observations have been made. At the time of writing there is a personnel of 28 members, 8 of whom are physicians, which includes pediatricians, an obstetrician, an orthopedist, and specialists in roentgenology, psychology, anthropometry, nutrition and dentistry, as well as nurses, social service workers, technicians and secretaries.

The material under consideration consists of a normal child series in which 224 children are actively enrolled, a normal pregnancy series (1935-1937) in which 86 cases were studied, and a premature birth series (begun in 1934) which includes 47 children who are still being followed. The second half of the monograph is a detailed report on the studies of 2 sisters, each of whom has 3 children. The remarkably complete family analysis and the detailed nutrition studies are of especial interest.

This publication should be read by all those who will be interested in the subsequent reports from the Center.

J. R.

TEXTBOOK OF PATHOLOGY. A CORRELATION OF CLINICAL OBSERVATIONS AND PATHOLOGICAL FINDINGS. By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine; Chief Visiting Pathologist, Charity Hospital, New Orleans, etc., and HERBERT J. SCHATTENBERG, M.D., Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine; Visiting Pathologist, Charity Hospital, New Orleans. Pp. 681; 383 illustrations and 13 colored plates. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.50.

In a field already crowded with one-volume textbooks, new books on pathology continue to arrive periodically. The Duval and Schattenberg contribution aims to correlate clinical observations and pathologic findings, a viewpoint given modern emphasis in the several texts of Professor Boyd. This trend, carried to an almost incredible extreme by Smith and Gault, threatens to relegate the science of pathology forever into the mean and minor rôle of a lowly handmaiden to clinical medicine. It is discouraging to meet, on turning the first page, a faulty understanding of Menken's recent work on inflammation and an unbelievable misquotation of his term "leukotaxine" as "leukotoxine."

General pathology is dealt with in a cursory, often inexact and sometimes quite erroneous manner, as, for instance the description of hyaline degeneration as due to a "deposition in the tissues of a peculiar albuminous substance known as hyaline." The special pathology section offers nothing new and the correlations with clinical observations contain little more than is usually

given in descriptive pathology. The bibliography is brief and restricted entirely to publications in English. The book is plentifully provided with plates of mediocre quality.

With revised editions of such sound textbooks as Karsner's and MacCallum's available, the Reviewer cannot find anything in this new work which would lead him to recommend its presence in the library of student, physician or pathologist.

D. C.

MAN AGAINST MICROBE. By JOSEPH W. BIGGER, Sc.D., M.D., F.R.C.P.I., M.R.C.P. (Lond.), Professor of Bacteriology and Preventive Medicine, Trinity College, University of Dublin. Pp. 304; 16 illustrations and 18 plates. New York: The Macmillan Co. Price, \$2.50.

THE book is written for "a person of some education, but not a scientist" and should be very interesting to a layman. The author not only describes somewhat man's fight against microbes but also, in non-technical terms, briefly describes what microbes are, how they are studied by microbiologists, how they are identified and how man acquires his microbes. The author has obtained his material from authentic sources and this book could very profitably be included in reading lists for high school and college students.

H. M

NEW BOOKS.

The Surgery of Pain. By RENÉ LERICHE, M.D. (LYON), LL.D. (GLASGOW), F.R.C.S. (ENG.), (HON. CAUSA), etc., Professor of Clinical Surgery, University of Strasbourg. Translated and Edited by ARCHIBALD YOUNG, B.Sc., M.B., C.M., F.R.F.P.S.G., F.A.C.S. (HON.), M.D. (STRASBOURG), (HON. CAUSA), etc., Regius Professor of Surgery, University of Glasgow; Visiting Surgeon, Western Infirmary, Glasgow. Pp. 512; 18 illustrations. Baltimore: The Williams & Wilkins Company (A William Wood Book), 1939. Price, \$6.50.

The Journal of Endocrinology, Vol. 1, No. 1, June, 1939. A new journal to be devoted to the publication of papers on endocrinological subjects. Edited by E. C. DODDS. Assistant Editor: R. L. NOBLE. Editorial Board: P. M. F. BISHOP, C. R. HARRINGTON, G. F. MARRIAN, A. S. PARKES, F. G. YOUNG, S. ZUCKERMAN. Pp. 116; many illustrations. London and New York: Oxford University Press, 1939. Price, 10s. per copy (30s. per vol. or \$6 in U. S.).

Perspectives in Biochemistry. Thirty-one Essays presented to Sir Frederick Gowland Hopkins by past and present members of his Laboratory. Edited by JOSEPH NEEDHAM and DAVID E. GREEN. Pp. 361; illustrated. Cambridge: At the University Press; New York: The Macmillan Company, 1939 (Fourth Impression). Price, \$4.75.

Hay Fever, What to Do About It! By HARRY S. BERNTON, M.D., F.A.C.P., Clinical Specialist in Allergy Bureau of Chemistry and Soils, United States Department of Agriculture; Professor of Hygiene, School of Medicine, Georgetown University; Allergist to the Providence Hospital, Washington, D. C., etc. Pp. 76; illustrated. Washington, D. C.: Ransdell, Inc., 1939. Price, \$1.00.

Not a treatise on hay fever, but useful information about certain aspects of hay fever for those afflicted with this disease.

R. K.

Menstrual Disorders. Pathology, Diagnosis and Treatment. By C. FREDERIC FLUHMANN, B.A., M.D., C.M., Associate Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco; Assistant Visiting Obstetrician and Gynecologist to Lane and Stanford University Hospitals, etc. Pp. 329; 119 illustrations. Philadelphia: W. B. Saunders Company, 1939. Price, \$5.00.

- Cardiovascular Diseases. Their Diagnosis and Treatment.* By DAVID SCHERF, M.D., and LINN J. BOYD, M.D., F.A.C.P., Associate Professor of Clinical Medicine and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals. Pp. 458; 10 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$6.25.
- Pneumonia. With Special Reference to Pneumococcus Lobar Pneumonia.* By RODERICK HEFFRON, M.D., Medical Associate, The Commonwealth Fund; Formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 1086; 18 figures, 181 tables and several maps. New York: The Commonwealth Fund, 1939. Price, \$4.50.
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PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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THE VAGINA.

Artificial Vagina. There has been a definite tendency of late to get away from the Schubert and Baldwin operations in cases in which an artificial vagina must be made. Such operations were reasonably satisfactory, but since they involved resection of the rectum or lower ileum, they were accompanied by a mortality rate, which, although not excessively high, carried too great a risk for an operation which is not a life-saving procedure. It is generally agreed as stated by Dannreuther⁵ that surgical interference is justified in a young, attractive girl with secondary sex characteristics and sex urge, particularly if contemplating matrimony and who is so unfortunate as to have been born without a vagina. He has performed and recommends the Frank-Geist operation which includes three distinct operative steps, with interspersed minor procedures, numerous dressings and meticulous attention to detail. The first operation consists of making a skin flap on the inner aspect of the thigh $6\frac{1}{2}$ inches long and 3 inches wide and converting it into a pedicle tube, closing the adjacent edges under the tube. Four weeks later the distal attachment of the pedicle is severed from the thigh and the undersurface of the tube is reopened throughout its entire length. A space is then dissected between the bladder and rectum into which the pedicled flap is inserted after suturing it over a vaginal plug with the skin surface on the inside. The lower edge of the transplant is sutured to the vaginal outlet and the plug is maintained in place by means of a rubber sponge and tight binder. After 3 more weeks the attached end of the flap is divided a little at a time. The patient is discharged from the hospital 2 weeks later although the vaginal plug is worn continuously for several weeks thereafter. A vaginal dilator must be passed every day for a year to prevent contraction and if the patient does not marry, the plug should be worn at night. This operation has also been endorsed by Flynn and Duckett⁹ who state that while the operative technique is of great importance, the postoperative management must be rigidly observed, since the chief cause of failure is scar formation and contracture which rapidly

close the lumen of the new canal. Dilatation should be begun early, repeated frequently and prolonged indefinitely.

This type of operation has been modified by Douglass⁷ so that it can be performed in one stage and the patient discharged from the hospital in 1 month. He makes four flaps, two from the labia minora and two from the inner surface of the thighs and these are sutured into a prepared vaginal space and held in place by a pack of vaseline gauze. Although he reports only 1 case, the end result was satisfactory and obviously considerable time and trouble was saved.

In the case reported by Glowinski¹¹ the peritoneum of the pouch of Douglas was used in the construction of an artificial vagina. It is interesting to note that the patient was 33 years old and had been married 3 years before she sought surgical aid. In addition to an absent vagina the uterus was also absent. The operation consisted of a transverse incision at the site where the vagina should have been, followed by blunt dissection upward between the rectum and bladder until the peritoneum was reached. A large Hegar dilator was placed well up in this canal and held there tightly. The abdomen was then opened through a transverse incision just above the symphysis and the place where the Hegar dilator was pushing against the peritoneum of the pelvis was exposed. The peritoneum at this site was incised, mobilized and by means of long catgut sutures was drawn down into the previously prepared vaginal canal and sutured to the structures at the vagina outlet which had also been previously mobilized. A large tampon was placed in this new canal from the abdominal opening and the peritoneum was closed over it, thus forming a small peritoneal sac separate from the general abdominal cavity. The abdomen was then closed in the usual manner. The tampon was allowed to remain for 4 days after which saline douches were given. The vagina thus made admitted two fingers, was about 8 cm. long and it became covered with smooth epithelium. After 4 years of observation the vagina had not decreased in size and was perfectly satisfactory from the functional standpoint. The operation has a slight risk and can be used in any case where the uterus is also absent.

Based upon 32 cases reported, including 2 of his own, Barrows² believes that the Kirschner-Wagner operation has the advantages of no risk to life, simplicity of technique, no bad scars and short period of hospitalization. The operation consists of preparing a vaginal canal as in the other operations and inserting a rubber sponge prosthesis covered with Thiersch grafts with the skin surface inside. The resiliency of the rubber sponge keeps the grafts in contact with the raw walls of the canal for 8 or 10 days, at which time most of the grafts have taken. Postoperative dilatation is imperative.

Counseller⁴ has modified this operation by using a flexible rubber tube over which the graft is placed. The tube can be cut to any desired length, which is necessary because the length of the canal is variable, and is removed in from 10 to 14 days and replaced by a bakelite sound which is made especially for each patient. The sound is held in place by a sanitary belt and is worn for 6 months, being removed once daily for cleaning. He states that the management of vaginal stricture is

more difficult than that of congenital absence of the vagina. Extreme care must be used to avoid injury to the urethra, bladder and rectum, since it is necessary to form the new vaginal tract by sharp dissection through dense and often inflamed scar tissue. The cervix should be located if possible, so that the patient can again menstruate. When the cervix can be located, it is pulled into the rubber tube over which the graft is placed. The grafts then grow over the anterior and posterior vaults leaving the cervix exposed.

A simple method of constructing a vagina has been described by Wharton²⁷ based upon the principle that the vaginal epithelium has remarkable powers of proliferation and in a relatively short time will cover a raw surface. Another new feature is the use of a plug or mold to keep the new vaginal cavity open, this mold being composed of a rubber condom filled with some fairly firm substance such as paraffin or balsa wood. The operation consists of dissecting a space between the bladder and rectum and then introducing the vaginal mold, the whole operation taking only 10 or 15 minutes. The mold is allowed to remain in the vagina for 3 weeks, during which time it requires no attention except to be sure that it does not come out. The patient is kept in bed as long as the condom is in place. There are two important details to observe in preparing the vaginal canal. First, the space must be larger than one expects it to be eventually, to allow for contraction during convalescence due to the slipping of the mold or pressure from surrounding organs. The second point of importance is to have good hemostasis, paying especial attention to the vaginal branches of the uterine arteries, which are at the level of the broad ligament on each side. The condom mold should be flush with the vestibule after it has been inserted and the perineum must be inspected several times daily to see that it remains in place and is causing no edema or pressure changes. The patient is advised to change her position in bed frequently so that the weight of the vaginal form will be evenly distributed. After leaving the hospital coitus is prohibited until 2 or 3 months have passed or until the vaginal epithelium has become thick and tough. During this time a loose vaginal plug is worn at night. If the first operation does not provide a vagina of satisfactory size it can easily be enlarged subsequently. Since the vaginal space is lined by epithelium which proliferates from the vestibule or the rudimentary vagina, this operation is feasible only when there is some vaginal epithelium to start with and he hesitates to recommend it when there is complete absence of all mucous membrane. He has performed the operation in 4 cases, in 2 of whom follow-up results have been satisfactory.

As simple as this operation seems, the method suggested by Frank¹⁰ is even simpler, since no operation involving incision is done. He has been struck by the very thin tissues which separate the rectum from the bladder in these cases and he has attempted to force inward the mucous membrane in the introital region without incision and has found that a vagina may be readily established. The first object is to establish a narrow canal at least $2\frac{1}{2}$ inches long as quickly as possible. After this depth has been attained, enlargement of the canal follows. The

first step is important. A narrow pyrex tube, 0.8 cm. outside diameter, is introduced by the physician in the hymeneal region in a direction backward and inward with the patient in the lithotomy position. The patient is carefully taught to perform this maneuver 3 times daily for at least $\frac{1}{2}$ hour for 1 week. This is important in order to stretch the mucosa so that further measures do not distort and dilate the urinary meatus. After the first week, the patient inserts the tube as before and then changes the direction of insertion in a line paralleling the normal axis of the vagina. The tube is held in place for $\frac{1}{2}$ hour morning and evening. Usually in from 2 to 4 weeks a sufficient depression permitting the retention of a 3-inch-long tube has been attained. This is kept in place at night by a binder. The patients are warned not to apply excessive force as evidenced by bloody spotting. The diameter of the tube is gradually increased until a 2 cm. size is reached and this is kept in the vagina every night for from 8 to 10 hours until marriage. He reports the use of this method in 6 patients in only 1 of whom was there a failure.

Gonorrheal Vaginitis. An unusual amount of attention has been paid to the subject of gonorrheal vaginitis in recent years and a review of this kind can do no more than attempt to present the conclusions reached by some of the leaders in this field. From the evidence obtained in a large series of cases in which smears and cultures were made, Ruys²² of Amsterdam believes that gonorrheal vaginitis occurs only in the acute form and is always complicated by gonorrhea of the rectum. It is recognized that in many cases of vaginitis there is no history of an acute attack. The children suffer from a chronic state of irritation with a varying degree of secretion. They often look pale and have a severe local inflammation, but in these cases the smears and cultures show different bacilli and cocci in varying quantities and it is difficult to conclude whether these bacteria are of etiologic importance or are merely secondary invaders. The success of hospital treatment in such children, Ruys believes, is due more to the improvement of the general health conditions than to local treatment. It should be remembered that foreign bodies and parasites in the vagina can give rise to severe local symptoms. In the series reported which were very carefully studied, only 57 of the 292 children with vaginitis actually had gonorrhea.

There has been great interest in the estrin treatment of this condition since Lewis¹⁷ presented it 6 years ago and there has been considerable speculation as to how it works. Lewis and Weinstein¹⁹ have found that the administration of estrin to children renders the vaginal secretions strongly acid and they believe that this acidity in all likelihood is the important factor. Lewis and Adler¹⁸ state that in normal children the reaction of the vaginal secretions is nearly neutral (usually between pH 6.8 and 8.4) and when the vaginal mucosa reacts to estrogenic substances the secretions become markedly acid (pH 4.8 to 6). *In vitro* the gonococcus grows best in a faintly alkaline medium (pH 7.2 to 7.6). If this is rendered acid very gradually over a period of days or weeks these organisms will rarely adapt themselves to a medium as acid as pH 6 to 6.2. The production of acidity in the vagina is good evidence

of the effectiveness of estrin, it is easily determined and is much simpler than the taking of biopsies for the determination of epithelial cornification as was done in the early work.

The cure of 175 patients with gonorrheal vaginitis by the use of estrin is reported by Te Linde.²⁶ Except for 16 who received the product hypodermically in oil, all were treated by the use of vaginal suppositories. He has failed to encounter a patient who did not get well by this method of treatment and naturally he considers it a very satisfactory method of handling these little patients. A follow-up examination of the first 100 patients, from 3 months to 2½ years after the last treatment, showed 98 of them well. There has been no clinical evidence of harm due to the treatment. He agrees in part with Lewis that the increased acidity brought about in the vagina by the action of the estrin is a factor in overcoming the infection, but since his results were not nearly so good when another acidifying suppository was used, he feels that there must be some other factor involved as well, probably the increased thickness of the vaginal epithelium which prevents reinfection of the subepithelial tissues and thus permits the inflammatory process in them to subside. He has found that by giving a suppository containing 600 international units daily, the vaginal epithelial response is noted in 13 days and the smears become permanently negative in 18 days. Treatment is usually continued for several days afterward so that the average total time of treatment is slightly less than 27 days. This is surely a different story from the days when we treated these patients for months or years, often without permanent relief.

In the opinion of Mazer and Shechter²⁰ the good effect of estrogenic substances in this disease lies in its ability to create a temporary maturity of the vagina and thus render it resistant to pathogenic bacteria, but they emphasize that the pH of the vaginal secretions must be reduced below 6. To safeguard against recurrence of the infection, treatment should be continued for 8 weeks even though there is earlier clinical and bacteriologic cure. In their series, hypodermic injections cured 78 of 81 children with a 10% incidence of recurrence; vaginal suppositories cured 33 of 34 children without any recurrence in the 26 children who were observed for a long time; oral treatment was ineffective in 3 children who received as much as 1500 rat units daily for a period of 8 weeks. Side effects, such as pubic hair, uterine bleeding and enlargement of the breasts, are temporary and are more frequently encountered with hypodermic than with local treatment.

Since sulphanilamide was found to be of value in gonorrhea soon after it was presented to the profession, it is quite natural that it should have been tried in the treatment of vaginitis due to this organism. In reporting their experiences with this drug at the Cook County Hospital in Chicago, Hoffman, Schneider, Blatt and Herrold¹⁵ have not obtained outstanding results. In a series of 25 patients who were given sulphanilamide, 7 were cured in an average of 17.3 days and 9 more in an average of 42.9 days. Only 2 of the 9 remaining patients were cured by additional administration of the drug. A standard dose was used in all and the results suggest the futility of the continuation

of more than two standard courses of treatment. The children tolerated the drug extremely well as compared to adults.

Schauffler, Kanzler and Schauffler²³ have collected 261 cases of vaginitis treated by sulphanilamide in 18 teaching institutions and by 10 individual observers and have come to the conclusion that hospitalization is necessary in giving this type of treatment. Continuous medication, rest, blood studies and careful observation will remain essential until the limits of safety can be more clearly delineated. Since from all other angles hospitalization in this contagious disease is definitely contraindicated, this must be considered a disadvantage. Of the collected opinions in this study, the total consensus was only 55% favorable for the drug, it being regarded as inferior to other methods of treatment by the majority and nearly one-half will discontinue its use in this connection. Low dosage and failure to maintain the blood concentration may be responsible for some of the poor results, but the possibility of a connection between the desired acid reaction of the vagina and the unfavorable effect of an acid reaction on the action of sulphanilamide should be considered.

For purposes of comparison, the series of 112 cases reported by Burpee, Robinow and Leslie³ is of interest, as several methods of treatment were employed. The intramuscular injection of estrin in oil gave 41 cures in 47 cases, but in 5 of these there were later recurrences. Five patients treated by a combination of estrin and 1% silver nitrate jelly locally were cured with no recurrences. Nineteen cases received fever therapy alone, produced either by injection of typhoid vaccine or by the Kettering hypertherm, with 8 cures and no recurrences. Twenty-two patients received sulphanilamide alone and of these 11 were cured and there was 1 recurrence, all of the cures being obtained in less than 2 weeks. Increase of the dose, prolongation of the treatment and combination with fever therapy did not improve the results.

Trichomonas Vaginalis Vaginitis. In an article which evaluates the various types of treatment of vaginitis associated with *Trichomonas vaginalis*, Hesseltine¹³ states that at the present time the drastic scrubbing procedures of a few years ago have almost been replaced by a dry technique, with the patient self-administering much of the treatment. He compared the effect obtained by the use of 3 arsenical preparations, 1 silver picrate and 2 lactose combinations, the control patients receiving the preparation minus the supposed active ingredient. In order to be considered cured, the patient had to go through two consecutive menstrual periods without treatment, remain free from symptoms and present no clinical or laboratory evidence of the disease. He found that good results may be obtained with various agents in approximately 85 to 90% of the patients, while the remaining 10 to 15% may not remain relieved or may even fail to be improved. Probably in from 8 to 15% of the cases particular care should be taken to eliminate foci of infection from the patient's rectum, urethra or bladder, or from the husband's urethra or prostate.

Since protozoa in general are sensitive to variations in osmotic pressure of the surrounding medium, it occurred to Rosenthal, Schwartz and Kaldor²¹ that this vaginal protozoön may also be affected by such

variations and they decided to study the action on it of hypertonic salt solution. They experimented with four dilutions of sodium chloride, namely 3, 6, 12 and 25%. The 3 and 6% salt solutions apparently did not affect the parasite, but entirely different pictures were obtained when salt solutions of 12 and 25% were used. The motility of the parasites stopped instantaneously and their shape underwent a radical change. The parasites became shrunken and crenated and to all appearances were dead. When the parasites were transferred immediately after their inactivation from a 12% solution into a physiologic solution their normal shape and motility were restored. The 25% salt solution, however, made the inactivation permanent and irreversible. On the basis of these laboratory findings they treated over 50 cases with a 25% salt solution douche and in nearly all cases the relief was prompt after 1 or 2 daily douches. The itch disappeared, the discharge became scanty, thin in character and odorless, or even disappeared entirely, and the vaginal mucosa assumed a normal appearance. In 30 cases, no more organisms could be found after 2 or 3 douches. Twenty-four cases showed complete absence of live parasites after 1 week of daily douches and 2 cases required 2 weeks of daily douches to bring about the disappearance of the parasites.

In order to determine the incidence of *Trichomonas vaginalis* and its pathogenicity, Jacoby and Der Brucke¹⁶ examined 300 consecutive patients for the organism and found them in 50 (16.6%). Of the patients in whom the organism was found, 16% had no discharge of any kind and 24% had only a slight discharge. Only a third of the patients complained of itching or had any evidence of vaginitis. They believe that the trichomonas is essentially a surface parasite and can readily be washed away by a simple douche and that it is a non-pathogenic invader of the normal or diseased vaginal tract. If it invades a normal vagina, no symptoms are produced, while in the diseased vagina the symptoms are those of the disease present and are not initiated by the trichomonas. Treatment for its destruction is not necessary in their opinion, but effective treatment of the underlying inflammatory condition, cervical or vaginal, will cure the patient. The treatment that yielded the best results in their hands was that directed toward the elimination of the chronic congestive condition in the pelvis and not paying any attention to the trichomonas itself. With the eradication of the causative factor in the pelvis and eliminating stasis, all of the symptoms disappeared in 75% and the organisms disappeared in 91.6% of their cases.

It has long been known that trichomonads are found in other locations than in the vagina. Among 58 women examined by Stein and Cope,²⁵ all of them having *Trichomonas vaginalis* vaginitis, trichomonads were found in the gums in 3, in the stools in 3, and in the catheterized urine in 5. It is apparent from this observation that there is no causal relationship between the vaginal incidence and that of other common sites of trichomonads in the body. Moreover, there are cultural characteristics which differentiate the vaginal trichomonas from the buccal and intestinal types. While occasional instances of infection of husband and wife, and 1 case of infection of 3 female members of the same family

are reported, the evidence is insufficient to conclude that it is directly transmitted from person to person. The source of the trichomonads in the vagina is unknown and it is unlikely that they may migrate from the other common sites in the body. In spite of other reports, they still believe that *Trichomonas vaginalis* is pathogenic, that it is a specific species and that it is apparently in symbiosis with the bacteria commonly found in the vagina.

Hibbert and Falls¹⁴ present evidence which they believe demonstrates that the *Streptococcus subacidus* is the causative factor in this type of vaginitis. They recall that *Trichomonas vaginalis* may be present for long periods of time in the vaginal secretion without producing symptoms, and conversely, there are many cases having all the symptoms of trichomonas vaginitis which fail repeatedly to reveal the presence of the parasite in the discharge. Having isolated the *Streptococcus subacidus* from the discharge of their patients, they inoculated 5 other patients with a pure culture of the organism, in 4 of which definite vaginitis was produced as evidenced by intense redness of the cervix, vaginal mucosa and vulva and a gray-white sticky discharge and the patients all complained of tenderness, burning and itching. These patients were then treated by means of the application of a broth filtrate of the *Streptococcus subacidus* to the cervix and vagina, together with intracutaneous injection of a vaccine made from this organism. The treatments were given once a week and all were cured in from 4 to 7 treatments. From all of the foregoing opinions it may be gathered that while there is not unanimity as to the importance of the protozoön, the tendency is to treat the associated vaginitis with much milder methods than formerly or even to ignore it as such and treat the general condition of the patient.

Senile Vaginitis. After an artificial or natural menopause there are physiologic atrophic changes which occur in the genital organs which consist of a shortening and constriction of the vagina, particularly at the introitus, together with a loss of elasticity and distensibility of the vaginal walls. Davis⁶ states that senile vaginitis follows an inflammation superimposed on the atrophic mucosa of the vagina. The exciting factor may be an irritating uterine discharge which macerates the atrophic vaginal epithelium or a recurring minor trauma which injures it. The usual pathogenic organisms in the vagina invade these denuded unprotected areas and start an inflammation, causing superficial ulcerations or erosions which appear as small punctate hemorrhagic areas. Sometimes the denuded areas become fused together and form adhesions which, in severe cases, may hide the cervix or even close the vaginal lumen. The symptoms of this type of vaginitis are discharge and burning, pelvic pain, burning on urination and pruritus. Assuming that the changes in senile vaginitis would disappear if the mucosa could be restored to the type present during active sex life, Davis thought it worth while to try the effect of estrogenic hormones in such cases. He treated his patients with 100 rat units of estrogenic hormone subcutaneously 3 times weekly and in addition a suppository containing 75 rat units was inserted into the vagina every night. The average patient was treated for 6 weeks, although in most instances

the symptoms disappeared after 10 days. The changes in the vaginal mucosa as the result of this treatment were most interesting. The inactive basal cells began to proliferate, the cells soon contained an abundance of glycogen and the inflammatory foci beneath the squamous epithelium disappeared. These changes, however, were not permanent. Several weeks after the cessation of treatment the mucosa rapidly returned to its previous condition of atrophy but the patient's symptoms did not return unless she had not received enough treatment and some inflammation still remained. If trauma and infection are again introduced, senile vaginitis will undoubtedly recur.

Inquiring into the dietary habits of 50 patients with senile vaginitis, Simpson and Mason²⁴ found that the majority existed largely upon a diet consisting of toast and coffee for breakfast, thin soup and side meat, corn bread and jam for lunch, some form of pork and one or two vegetables for supper. Sweets and desserts were prominent in all the diets. In many instances distinct lack of desire for butter, eggs, fresh meat and milk was noted. Such diets, obviously low in vitamin A, are peculiar to elderly women. In some patients, chronic digestive disturbances and habitual use of mineral oil were also suggestive of impaired absorption and utilization of vitamin A from the diet. For this reason they treated their patients by the administration of cod- or halibut-liver oil 3 times daily with or without the use of plain tap water douches. The treatment proved unusually effective in producing rapid relief of symptoms and in the gross and histologic repair of the vaginal mucosa.

A different method of approach in the treatment of this disease has been taken by Adair and Hesseltine,¹ who believe that in bacterial infections the epithelial cells and their glycogen-like content need stimulation as well as the protection of an increased vaginal acidity. For this purpose they used a mixture of lactose (95%) and citric acid (5%) which the patient inserts into the vagina each night. This mixture favors the growth of the normal vaginal bacilli and senile vaginitis cases have been cured by this method in an average of 4.5 months. From the above diverse methods of treatment it may be observed that the basic principles of all of them depend upon improving the nutrition of the vagina and the avoidance of trauma and reinfection.

Vaginal Hernia. In presenting a case of vaginal hernia, Hall¹² has reviewed the literature of this rare condition and has assembled some interesting facts. In this type of hernia the peritoneum is pushed downward through the pelvic floor into the vaginal vault or along the wall between the vagina and the rectum or bladder, sometimes extending between them all the way to the perineum and it is of interest in the differential diagnosis of cystocele and rectocele and as a complication of uterine prolapse. These hernias all have a separate peritoneal sac, which cystocele and rectocele do not have, and a definite ring which is absent in uterine prolapse. Most masses in the upper part of the vagina are first considered rectoceles. However, one should note that the hernia appears when the patient stands, coughs or strains, disappears when she is in a recumbent position, has a definite hernial ring, gurgles on manual replacement of the bowel and has no connection with the rectum, although it may be accompanied by a rectocele.

Usually the hernia merely causes some discomfort but in 25% of the cases there are complications and in one-third of these there is a fatal termination. If the condition develops during labor, the signs may be those of shock and intestinal obstruction. The treatment in such a case is immediate return of the head and reduction of the hernia. Obstruction and strangulation from other causes demand immediate surgery. Operation may be done by the abdominal, perineal or combined approach and the insertion of ureteral catheters before operation is advised.

Cancer of Vagina. A study based upon 37 cases of primary cancer of the vagina has been presented by Emmert,⁸ the youngest patient being 26, the oldest 82 (average age, 53 years). Previous labors seem to have little to do with the etiology, since 7 of the patients were nulliparous; and if parity had any influence, primary cancer should be much more common, its incidence in this study being only about 1% of genital cancer. Of the 37 patients, 4 were treated purely palliatively with acetone, because their condition was too far advanced for any hope of cure. Radium treatment was given to 21 patients of whom 19 were followed. Four of these are alive 11, 8, 7 and 1 years, respectively, after treatment. Five patients were subjected to radical colpectomy and vaginal hysterectomy. There was 1 postoperative death and 2 of the others are alive 6½ and 1½ years later; a third case is alive with recurrence. From his study he admits that the hopes based on operation and radium therapy in this disease have not yet been fulfilled since the curability rate is but 12%. He advises that in the early stages of the disease a really radical operation should be performed, while radium with or without Roentgen rays should be applied in the more advanced cases.

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DERMATOLOGY AND SYPHILOLOGY.

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**THE PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS
REACTION MECHANISMS.**

As Foster Kennedy^{59a} remarked in discussing the emotional background of the skin, "If one were to speak of and stand by only those things which one knows, there would be a great silence in the world." He concedes, however, that deliberations on the subject keep the mind active, even if they do not always cure the disease. The notable increase in significant work in the field of psychosomatic relations extends to the skin no less than and perhaps more than to other structures. In naming some of the important workers and summaries, a gesture of admiration and respect must go to H. Flanders Dunbar,³² for her monumental summarization of the entire literature of the psychosomatic field in which the cutaneous division occupies 38 of 432 pages of text, with 120 bibliographic titles.

The father of cutaneous neuropsychiatry, so to speak, is W. Theodore Sack⁸⁶ whose summarization of the subject appears in the Jadassohn Handbuch. The Barber-Gillespie^{5,38} group at Guy's Hospital, including Drake,^{30a,b} Rogerson,^{81,82} and Strauss,⁹⁹ constitutes probably the most important group now active in the field. In this country Klaunder^{60a-d} and Hazen⁴⁸ have initiated and kept alive much of the American interest in the subject. Becker^{8a,b,76,101} and his co-workers have concerned themselves with functional dermatology from the neurovascular standpoint. Many highly significant investigations have come by way of fundamental vascular and neural physiology, as in the Lewis-Dale^{24,25,67} conception applied to the skin. Psychoneurogenous considerations have been hobby interests of various clinics such as that of Bloch¹² (Zurich) and the University of Pennsylvania.^{9,92a-f,93,95-98} The extended British and German work on asthma has established important correlations in the cutaneous field. Psychotherapy and hypnosis, the latter especially, have been studied by Kartamischew,^{56a-e} Wisch¹⁰⁶ and Bunnemann.¹⁸ It is impossible to overestimate the importance of the contributions of workers in what at first glance seems to be unrelated fields, such as that of gastro-intestinal physiology and cutaneous mycology and bacteriology. In general, allergists interested

in dermatology have seen few neuropsychiatric bearings (Walzer¹⁰³) with the exception of Duke^{31a} (emotional urticaria).

Fundamental Physiologic-neurologic Linkage and Basic Mechanism—Vascular and Vasculo-visceral Fields.—Skin color as an expression of vasomotor and hence frequently emotional reactivity has had vigorous emphasis at the hands of all clinical observers. There has, however, been a notable deficiency of colorimetric studies of the influence of emotion on the vasomotor mechanism. One reason for this has been the slowness and cumbersomeness of spectrophotometry as demonstrated by the apparatus of Sheard⁴⁵ and others. It is possible that the improvement effected by Hardy⁴⁴ may make possible direct analysis of the emotional color changes, through the psychogalvanic reflex which has been thought to reflect the state of the terminal capillaries in the skin (Densham and Wells,^{27a,b} contradicted by Darrow²⁶). The notable possibilities of skin temperature study, which is a reflection of blood supply and vasomotor tone, are admirably illustrated by Mittelman and Wolff⁷⁴ who, with special apparatus under controlled temperature and other conditions, investigated the relations of mood, of the presence of observers, and of the repeated discussion of life situations in a subject with growing tension and despair. The discussion of impersonal topics; awareness and insight; moderate and intense emotional stress in normal subjects and in one with Graves' disease; the major temperature changes in the Raynaud syndrome; and the effects of sympathectomy were objectively studied. Ziegler and Cash¹⁰⁷ review a considerable literature. Their material was largely psychopathic; a wide variability of reaction was observed; the opinion was expressed that cerebral heat control is centered in the hypothalamus. Bazett's⁷ work on skin temperature is mainly on cerebral localization of heat centers (cats).

The Sweat Mechanism. The influence of sweat on the pH of the skin, on the concentration of secreted reducing bodies on the skin surface, and also in the case of certain glands (apocrine) of soluble proteins and odoriferous substances, is one of the important linkage mechanisms in the effect of emotion on pathologic conditions of the skin. Kuno's⁶⁴ excellent review of the physiology of human perspiration (1934) gives great weight to the emotional factor in sweating. The two embryologic groups of sweat glands, the apocrine and the eccrine, are clearly differentiated in their behavior by all students of the subject, and an excellent review of what is known of the physiology of the apocrine glands since Schiefferdecker's⁸⁷ fundamental investigation is given by Way and Memmesheimer.¹⁰⁴ The eccrine gland secretion is of a markedly lower pH than the apocrine, and it is the secretion of these glands over the largest part of the body surface which maintains quite largely the so-called acid defence mantle. The secretion of the apocrine sweat glands at a much higher pH is much more favorable to the growth of fungi and other infective organisms, and is an important factor in the localization and characteristics of certain dermatoses. Apocrine sweat gland distribution occurs only in the hairy regions of the axillæ, the mons veneris, the perineal and circumanal regions and the anterior abdominal wall and the aureola and hair follicles about the nipple.

Kuno⁶⁴ points out in summarizing a number of investigations that the weight of present-day effort tends to show that all sweating is centrally controlled through sympathetic fibers. Pituiritrin injected in the region of the hypothalamus *via* the cerebral ventricles gives rise to extraordinary sweating which does not occur when the drug is introduced in other ways (Cushing²³). The rôle of pituiritrin in the production of sweating is, however, by no means clear. The sweat secretion most obviously influenced by mental states is that of the palms, soles and axillæ. Kuno⁶⁴ considers this to be controlled by a special center in the midbrain, different from the general sweat control. Inhibition of sweating, like excitation of it, can occur under mental stress.

The interest attaching to the apocrine group of sweat glands arises particularly from their embryogenesis and close relation to the sexual mechanism. They develop at puberty, remain active throughout the larger part of the individual's life, and are markedly influenced by stimulation of the sexual, mental and nervous reactions. So marked is the relation of the apocrine glands to cyclical sexual phenomena in women that they have come to be regarded essentially as accessory sexual glands (Way and Memmesheimer¹⁰⁴). Loeschke⁶⁸ noticed their participation in the sexual cycle; Waelsch,¹⁰² Kayser⁵⁷ and Seitz⁸⁹ confirmed these observations, and the studies of Herzenberg⁴⁹ have led to the belief that apocrine glands are influenced by physiologic rather than pathologic sexual occurrences. Occasional case reports, and in all probability much unreported material attest the great psychogenetic importance of abnormalities of apocrine sweat secretion. Gillespie,³⁸ for example, cites the case of a woman whose hyperhidrosis began with her engagement to marry a man whom she did not love, and continued because of the conflict between her sense of duty and her enforced dependence on her husband, with her desire to dissolve the marriage.

The observer has no difficulty parenthetically speaking, in observing the connection between vulvar sweating, sweating about the umbilicus, and sweating in the axilla in women, and various sexual states and episodes, including deprivation of sexual relations, serious grades of conflict involving the fidelity of the husband, and so forth. Unfortunately, most of this material has not as yet been subjected to critical analysis by quantitative test of the amount of sweat secretion in known areas under varying circumstances, and so forth.

Sweating of the palms and soles is well recognized as a close associate of mental effort of many kinds, including even so simple a matter as the addition of a column of figures. That it can be closely associated with psychogenous states is apparent in those patients whose palms never sweat except under special circumstances such as taking leave of a stranger, taking a special form of examination written or oral, and so on. The reported material in this field is small and far less than the importance and experimental possibilities of the work would make possible. A recent technical contribution to the experimental approach has been made by Buley¹⁷ whose apparatus permits the collection of sweat from individual glands and quite accurate estimates of the rate of secretion under various stimuli.

The Gastro-intestinal Mechanism. Stokes and Pillsbury⁹⁶ attempted to erect a theory of gastro-intestinal mechanism in emotional and nervous manifestations on the skin based largely upon the work of Spie-thoff,⁹⁰ Ehrmann,³⁴ Ryle and Barber,⁸⁵ Brown¹⁶ and Eastwood,³³ Knowles and Decker,⁶¹ Rulison,⁸⁴ Ayres⁴ and others, from the dermatologic side, and Alvarez,² Carlson,²¹ Hornborg⁵² and Bogen,¹³ Schrottenbach,⁸⁸ Cannon²⁰ and several observers working with hypnosis, including Bennett and Venables¹⁰ and Heyer.⁵⁰ In addition to the contributions dealing largely with gastric hypoacidity under emotional stress, they invoked the effect of gastric secretion on the duodenal bacteriologic flora (Ricen, Sears and Downing⁸⁰), relations between gastric acidity and blood uric acid (whose increase in certain conditions has been credited with etiologic importance), pointed out by Kurti and György;⁶⁵ effects on biliary stasis (Ivy,⁵⁵ Elman and McMaster³⁵); on carbohydrate metabolism (Freud and Saadi-Nazin³⁷); on pancreatic secretion (Oechsler⁷⁷); on peristaltic gradients and absorption (Burnett¹⁹, Alvarez and Freedlander³); on absorption of histamine-like substances (Kendall and Schmitt⁵⁸); avitaminosis (Koessler, Maurer and Loughlin⁶²) as factors of possible importance in the emotional linkage of gastro-intestinal behavior with the reactions of the skin. In addition, these authors call attention to the carbohydrate ingestion factor in gas bacillus proliferation, the work of numerous observers, including Irving and Ferguson⁵⁴ and Abrahamson and Miller¹ on the relation of intestinal pH to calcium absorption from the intestinal tract.

Observers of large experience such as Stockton⁹¹ and Alvarez² have repeatedly emphasized the importance of psychotherapy in diseases of the intestinal tract, and there is very little doubt that through the psychotherapeutic approach to the gastro-intestinal tract, much can be done with some of its abnormal contributions to the behavior of the skin. Weiss and Collins,¹⁰⁵ in an interesting study of vagotonia and sympathicotonia in relation to the gastro-intestinal tract, reiterate what has been recognized in the skin since Brill,¹⁵ that vagotonia and sympathicotonia can rarely be demonstrated as pure cases of one or the other. They provide a tabular account of the symptomatic accompaniments of vagotonia and of sympathicotonia that should be helpful to the dermatologist called upon to deal with cutaneous conditions in which one or the other of these neurogenous groups of constitutional symptoms appear. Desaux and Antoine,²⁸ in a suggestive study entitled "Reactions of the Skin to Nerve Reflexes Originating in the Stomach and Intestines in the Adult," lay particular stress on the ability of local pain arising from various causes to give rise to the disturbances of blood flow which probably influence pruritus, and serve as the origin of scratching and of neurodermatitis. They maintain that dilatation of the stomach is capable of producing marked responses both in the sweating and the sebaceous secretory mechanisms of the face. They concede the great importance of the well-known vasodilator effects produced by the gastro-intestinal tract, particularly in the flush area of the face, but recognize no clearly understood mechanism. Menninger,⁷² in an interesting discussion of functional disorders of the gastro-intestinal tract, correlates gastro-intestinal symptomatology and function with the personality characteristics of the individual in a way

highly interesting and suggestive to students of the eczema-asthma-hay fever complex with its attendant personality characteristics. The aggressiveness, independence, and ambition of certain gastro-intestinal neurotic types which he regards as overcompensation for a repressed desire to be dependent, to be loved and to be fed, fits in singularly well with the psychologic characteristics of a large group of eczema-asthma-hay fever patients, as described by Rogerson,^{81,82} Strauss⁹⁹ and others. In Menninger's⁷² studies of colitis it is more difficult to find appropriate reflexes on the cutaneous behavior and his views on constipation will probably be better appreciated by psychiatrists than dermatologists. His point, however, is well taken, that all individuals presenting the gastro-intestinal symptomatology frequently accompanying the eczema-asthma-hay fever complex and the various phases of neurodermitis, should have the benefit of an accurate, penetrating and detailed analysis of the psychologic component. "The treatment in all cases must be directed towards the total personality, and not merely towards the stomach or the intestines or the colon" (or the skin). Foster Kennedy,^{59b} in a discussion of the nervous relationships of the gastro-intestinal tract, rates this group of structures as the primary ego. He points out the ulcer tendencies of the parasympatheticotonic (vagotonic) individual under repressed emotion, anxiety and heavy responsibility without any direct reference, however, to possible skin correlations. His remark on the allergic relations of emotion—"Recently I was able to show that many allergic persons express their allergic reactions only when their sympathetic symptoms are, as it were, 'triggered' and made more sensitive by emotion," has undoubted dermatologic correlation and explains perhaps why in the eczema-asthma-hay fever complex the large number of allergic reactions, to foods especially, is so fluctuant and variable, and so frequently without significance for the patient's general or cutaneous condition.

Direct Neural and Neurovascular Mechanism. The Lewis-Dale Concept. The extremely important advances included in the work of Sir Thomas Lewis⁶⁷ on the "triple reaction" in its relation to herpetic, dermatitic, diffusely inflammatory and urticarial lesions in the skin has been welded with the work of Dale²⁵ and his associates on the function of acetylcholine as the chemical intermediary between the nerve terminus and the muscle fiber in the parasympathetic factor in the nervous control of circulation and other functions. Several notable papers based on these conceptions dealing particularly with urticaria as a "cholinergic" phenomenon deserve mention. Grant, Pearson and Comeau⁴¹ report observations on urticaria provoked by emotion, exercise and heat in which the clinical correlation described some time before by Duke^{31b} is adequately substantiated and the mechanism made clear. These observers found that the urticaria was provoked through efferent peripheral nerves when these were stimulated by emotion, by exercise or by warming the body.

The experimental technique involved the immersion of the legs of a patient with "heat urticaria" in hot water, after the circulation in one arm was obstructed. This was followed by a general urticaria except on the ischemic arm. If warming was stopped, the patient cooled, and the circulation restored; when the rash was subsiding an intense urti-

caria quickly developed on the previously ischemic arm. This indicated clearly that H-substance was released in the skin of the arm while its circulation was arrested, and in response to warming the legs. Grant and his associates adduced "further evidence of the release of H-substance during occlusion" by first congesting the arm before arresting its circulation and repeating the experiment just described. When the urticaria began to develop on the free arm, numerous bluish spots of local vasodilatation appeared in the skin of the congested and occluded arm. These spots were found to mark the places where the wheals quickly appeared when the circulation was restored. The authors believed that this indicated that the stimulus (H-substance) was released in the skin through the peripheral nerves, since the nerve constituted the only functional connection between the ischemic skin where H-substance is released and the body where the stimulus was applied. Blocking of the cutaneous nerves in 3 of the cases prevented the development of the urticaria in the area of distribution of the nerves in response to warming of the legs. They felt that this demonstration was satisfactory to indicate a neurogenic cause for the urticaria. The nerves involved were probably cholinergic since the urticaria was also provoked by choline derivatives given subcutaneously or applied locally. Accordingly, they felt that the urticaria appearing in response to warming the legs was "due to the release of acetylcholine in the skin as a result of the stimulation of cholinergic nerve fibers. This release of acetylcholine in turn leads to the liberation of H-substance from skin cells." Marchionini and Ottenstein⁷⁰ had previously suggested that sensitivity of the patient's skin to sweat was an important factor in the production of the urticaria, but Grant and his associates⁴¹ could find no evidence to support this idea. They further described a condition of unresponsiveness of the vessels. Hopkins, Kesten and Hazel,⁵¹ reporting on the clinically familiar emotionally induced urticaria, brought on by anger, were able to confirm the work of Grant and his associates⁴¹ and to extend the observations on urticaria produced by iontophoresis of mecholyl and intradermal injection of various choline derivatives. They confirm the significance of Duke's^{31c} classification of these patients into local and general reactors, and they state that the locally produced urticarias have no emotional foundation. In certain subjects (Harris, Lewis and Vaughan⁴⁶) passive transfer of these localized urticaria manifestations indicated that they were circulatory in origin, rather than neurogenous.

Metabolic Studies. There have been practically no notable contributions to this field in some time. Dunbar's³² review (38 pages) of the subject and its psychogenous relations contains practically no references to skin correlation. The skin reactivity of hyperthyroid individuals is apparently vascular; that of hypothyroid individuals has not been adequately investigated. The now well-recognized pronounced effect of emotion on sugar metabolism should have its cutaneous correlates, which, however, have had no investigative attention so far as we can ascertain. It would be extremely interesting to determine whether threshold diabetes and lowered sugar tolerance of older patients with long-standing dermatitis and skin infection have any relation to emotional and depressive states. Hypoglycemia has as yet

no etiologic place in cutaneous disease, yet it has very interesting emotional and conduct correlations.

Glaser,³⁹ confirmed by Kretschmer and Krüger,⁶³ demonstrated the possibility of influencing the calcium content of the blood by the suggestion of excitement or quieting influences under hypnosis; but again, no skin correlation despite the interest in calcium metabolism for dermatology, is suggested. Both Dunbar's³² studies of the literature and that of Stokes, Kulchar and Pillsbury⁹⁸ failed to find any report of significant general metabolic influence involving acid base equilibrium in urticaria.

Studies of the Pruritus Mechanism. The recent literature, such as it is, continues to emphasize the sympathetic mechanism of itching. Brack,¹⁴ in an extended and involved consideration of the mechanism of itching, draws a sharp distinction between a species of threshold susceptibility to itching (*Juckbereitschaft*) and actual itching itself. He points out that there is a normal threshold of capacity for itching present in practically all persons, and that it is capable of proceeding towards abnormality or heightened sensitiveness in the direction of either sympathetic or parasympathetic abnormality. His presentation contains interesting comments on the production of itching by slight invisible vasomotor changes in the skin, and correlates itching with the hemoclastic crisis in what he apparently considers an important etiologic relationship. The predisposing causes of itching work chiefly in the field of the *Juckbereitschaft*, and are often both more numerous and quite distinct from those responsible for the actual itching. In view of this clear separation of the itch problem into two subdivisions, Goldsmith's⁴⁰ observations on the clinical side in a study of dermatoses in patients with nervous diseases and those without are interesting. He points out that pruritus depends upon peripheral perceptors both for pain and touch; that itching is received centrally in the thalamus, the cortex apparently having little or nothing to do with it. He mentions the demonstration of central or thalamic itching in cases of thalamic tumor without peripheral manifestations. He further points out that there constantly occur in the normal skin slight itching or pricking sensations (minor expressions of the *Jucksbereitschaft*?) and that the degree of attention available for them is generally so slight that they pass unnoticed, and need to be greatly intensified in order to enter consciousness. His point that it is sometimes not the sensation of itching that is intensified but the attention, is extremely well taken. The most recent contribution on the condition is that of Bickford¹¹ who, on the basis of a study of histamine reaction in the skin, also points out that itching phenomena can be grouped into two categories: the actual itch itself which occurs at the site of the stimulus, and "itchy skin," which is the sensory reaction of the surrounding uninvolved area. Itchy skin, which may perhaps be compared to some extent to the *Jucksbereitschaft* of Brack¹⁴ arises through a local axonic pathway, separate from that which is responsible for hyperalgesia and for the vascular flare. Nerves responsible do not, he believes, belong to the sympathetic system. The itchy skin sensation may be abolished by a degree of asphyxia which leaves spontaneous itching unaffected. A similar dissociation may be produced by cooling and nerve shock. This,

he believes, indicates that the nerves carrying the two sensations are separate. The sensation of tickling shows a close association with that of itchy skin in his experiments. Spontaneous itching is not felt at the point at which pain to the prick of a pin is detected. The pain of tickling, spontaneous itching and itchy skin, are all conveyed in the anterolateral tracts of the cord, since they disappear when this is divided. A condition of the skin in which itching is inhibited is described. Inhibition is central in origin and probably produced through the pain nerves.

Milian,⁷³ in a recent review of the nature of eczema, argues from clinical observation and theoretical grounds, that itching must be not of peripheral but of central origin, arising in the sympathetic bulbo-medullary centers. The associated capillary dilatation, edema and secondary vesiculation are related to abnormal function of the sympathetic nervous mechanism in its threshold susceptibility to itching. Lortat-Jacob⁶⁰ demonstrates the definite association of the sympathetic nervous system and pruritus, erythema, and vesiculation in the background of contact allergy. His case, a 50-year-old woman, who had a more or less generalized eruption since 1929, had worked with synthetic vanilla since 1925. The patient gave a positive patch-test to vanilla on the left arm but not on the right. She was then given an intradermal test which evoked generalized itching and when pilocarpine was administered her eruption extended to the point of severe generalization. She was then given atropine, which caused the eruption to disappear, and the patch-test to the supposedly offending substance to become negative.

Central (Thalamic and Other) Mechanisms. Little advance beyond the scanty contributions of central neurophysiology reviewed by Stokes, Kulchar and Pillsbury⁹⁸ (1935) has appeared in subsequent literature on the skin. The observations on cholinergic urticaria associated with rage and other emotions probably come the nearest to suggesting the validity of the central mechanism with a peripheral neural pathway. The medulliadrenal syndrome of Cannon²⁰ is probably still the best organized concept with possible cutaneous correlates in the literature. A thoroughgoing and admirable technical review of hypothalamic correlation by Grinker,⁴² Ingram,⁵³ and Ranson⁷⁸ mentions not a single cutaneous expression of midbrain disturbance. In fact, the concept of centers itself still seems far from being established and influences such as fear, which are well recognized in the asthma field, for example, appear from physiologic studies to have not centers, but an unusually diffuse functional mechanism in the central nervous system. Bard⁶ demonstrates that the function of the cortex is primarily that of a damper or inhibitor, rather than an excitor of the discharge. Thus the nocturnal itch crisis and the urticarial and asthmatic outbursts may be conceived as explosions from an area or a focus as the cortical inhibitory influence is suspended. Cannon pointed out how the inhibition of expressions of emotion may be conceived as leading to correspondingly reduced visceral function—as perhaps in the lowered blood pressure, hypochlorhydria, inhibition of gastro-intestinal movement and secretion, asthenia and muscular weakness that accompany the effort to control such emotions—and are a part of the clinical back-

ground of neurodermatitides, vasomotor neuroses, neurovascular instability, and at times urticaria and rosacea. The conditioned reflex, too, could well have further study, for its relation to fear, to asthma, and to the urticarias seems sufficiently established for a psychiatric and psychologic as well as dermatologic approach. Crocker,²² years ago, described a still classical example of a woman whose urticaria attacks, originally provoked by meeting strangers, were finally brought on by the mere ringing of the door bell.

The study of postencephalitics from the standpoint of cutaneous functional abnormalities, especially of the sweat and sebaceous mechanisms, as suggested by the observations of Haxthausen⁴⁷ (though apparently unconfirmed by Rattner⁷⁹) is also a potential study field.

Skin Infections Conditioned by Psychogenous Elements. We have alluded in the discussion of vascular and sweat mechanisms to a probably important group of dermatoses influenced by the emotions through these structural and functional channels. No dermatologist of experience alert to psychoneurogenous factors has failed to observe the emotionally induced exacerbations of fungus and fungus-pyogenic infections of the hands and feet under the influence of emotion and emotional crises. The ups and downs of the intertriginous streptomycoses involving the areas of apocrine gland distribution in the skin can be readily observed in women under emotional and particularly sexual stress. Sulzberger¹⁰⁰ has even gone so far as to suggest, and not un-plausibly, that the prevalence of dermatophytosis in those who use locker-rooms, gymnasiums and swimming-pools is not alone a function of the presence of the organism but of the receptive state of those exposed, particularly with reference to hyperhidrosis and nervous tension. Gillespie³⁸ cured a proved case of fungus eruption of the hands by three interviews in which the patient's abnormal relation to his father was successfully adjusted. Stokes and Sternberg,⁹⁷ in discussing the etiologic background of acne, point out the effect of emotional stress on flares of what is an obvious combination of pyogenic and mycotic infection of the skin. They suggest on clinical evidence that a combination of vasomotor congestive or flush effect with the broadening of the allergic base of the individual under emotional stress is the probably etiologic mechanism. The flush or blush mechanism in particular, in its ability to maintain long-standing hyperemia of the face, unquestionably materially influences the infective phases of the rosacea syndrome, as well as of acne and, even as suggested by Stokes and Callaway,⁹⁴ of the recurrences and severity of lesions of chronic erythematous lupus.

Allergic and Psychoneurogenous Correlation in the Skin. The skepticism or indifference of American allergists to the possible psychoneurogenous correlations of allergic phenomena developed by German and British observers in the case of asthma is well illustrated by the total absence of articles or reference to psychoneurogenous correlates in literature reviews in one of the most important American journals of allergy. The work of Fock,³⁶ Moos,⁷⁵ Römer and Kleemann,⁸³ Laudenhimer,⁶⁶ and Hansen⁴³ should be applied to the allergic background of the eczema phase of the eczema-asthma-hay fever complex as well as other dermatoses. Hansen,⁴³ after critically reviewing the literature

and his own experience, denied to any form of psychotherapeutic approach the ability to alter the fundamental allergic background, and cited as evidence patients who had lost their symptomatic reactions to their allergens without losing their positive cutaneous tests. A much more crucial type of evidence for the influence of the psychogenous in allergic skin reactivity appeared with the work of Diehl and Heinichen.²⁹ Their ability to change the wheal reaction to an allergen in controlled conditions under hypnosis has now been confirmed by the observations of Marcus and Sahlgren⁷¹ who, in a 36-year-old female psychopath, succeeded in demonstrating that her cutaneous reactivity to a linoleum extract, to which she was sensitive, could be inhibited almost completely by suggesting under hypnosis that the injected allergen was another substance. The same inhibitions were obtained in the case of pollen extract, and it was found possible to inhibit the tuberculin reaction. A further study of dermatographism in her case demonstrated that the dermatographic wheal could be enlarged or suppressed under hypnosis. Kartamischew^{56c} describes a 41-year-old woman with malaria who was intolerant to quinine, plasmochin, euchinin, developing urticaria 4 hours after administration. This could be cleared almost immediately with morphine, which led the observer to the belief that the effect was psychic. Under hypnosis the patient was given quinine and told that it was salol, whereupon no urticaria appeared. The susceptibility to quinine was thereupon abolished by suggestion. It must be confessed that Kartamischew's remarkable efficiency with hypnosis, as described in other papers, inspires one with a desire for confirmation of these remarkable observations by other workers.

It is proposed to continue the subject in a subsequent review with an enumeration of the dermatoses currently accepted as having marked psychoneurogenous components, including a brief statement on each; with a consideration of psychotherapy, psychoanalysis, hypnosis, and suggestion under anesthesia in the treatment of the psychoneurogenous element and with a critique of current work and literature in this field.

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ORIGINAL ARTICLES.

CONSIDERATIONS BEARING ON THE TREATMENT OF
ARTHRITIS.*

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DEVELOPMENTS have taken place in our concept of the arthritic problem. The field is not dominated, as was so long the case, by the limited hypothesis that arthritis is due to focal infection alone. For many years this was regarded as the only factor to which attention need be given.

It was early apparent to a small number, however, because of the interest which these workers felt in certain physiologic aspects of the disease, that these other aspects or factors also exert determining influences. Now the profession can hear with equanimity, from an interesting recent study of 200 cases of rheumatoid arthritis, that chronic focal infection plays a "comparatively unimportant rôle."

However justified in fact such iconoclasticism toward focal infection may eventually prove to be, other phases of physiology are independently coming in for more attention. As long ago as 1920 the writer stated that any observer can satisfy himself that such an episode as pneumonia or pregnancy may result, at least temporarily, in escape from symptoms of arthritic disease. Other experiences led him to believe and teach that there are functional changes underlying arthritic disability which pave the way for organic change and are indeed not wholly irreversible.

This principle of reversibility is more or less accepted for fleeting rheumatic disability, such as is encountered in a stiff neck from which one recovers after a little aspirin but is largely ignored or overlooked in more advanced stages where it is, however, none the less operative.

* Presidential Address at the Annual Meeting of the American Rheumatism Association, St. Louis, May 15, 1939.

The arthritic is abnormal not only because of deviations within his joints but also because of deviations within his body elsewhere, more or less open to modification. Hench has recently well developed the hitherto buried observation that icterus may also initiate a dramatic escape from the symptoms of the disease.

It is refreshing to hear from him that "the pathologic physiology of rheumatoid arthritis is more rapidly reversible than previously supposed." Rawls⁶ has recently adduced evidence to the same end and many illustrations of the truth of this principle are to be observed.

Thus, for one example, on nearly every hand systemic rest is acknowledged to be the most useful single basic factor in treatment of both great types. But rest is not a simple entity; it is a mosaic of countless components, some of which may do harm as well as good, all of which are susceptible of more refined application than they are usually accorded. There is perhaps no fixed entity such as rest, *per se*, since rest is a relative term.

However, the processes comprised by rest can be analyzed and largely separated so as to permit of appropriate application. Rest to the nervous system, for example, is not a complete negation of activity. It is a specific prescription for a different kind of physiologic performance, which can even be abetted pharmacologically. Rest to the vascular system may be regarded equally specifically as an adjustment of physiologic requirements to the capacity of the system, especially the capillary beds.

The gastro-intestinal system may be made equally to perform, by rest, in a more effective manner and the processes of nutrition can be similarly bettered.

Undoubtedly a better concept would be obtained of that whereof rest consists, if, instead of a blanket prescription for rest, with all that is hidden and unobserved beneath it, the physician should explicitly order, severally and separately, the specific things which rest brings about. Probably few physicians could do this without study, and yet it illustrates only one of the therapeutic approaches to the arthritic problem.

Use of "rest" in this broad way, however, is not to be interpreted as a generic panacea for arthritics. It is brought forward rather as a comprehensive, though fragmentary, method of approaching that betterment of function, in many systems of the body, which makes toward a so-called reversal of the arthritic process. Such betterment of function is not necessarily optimal or complete when induced in this way alone and it is certain that treatment of arthritics cannot be reduced to a catchword, even one so important as "rest."

The chief point at issue is that without awaiting influences yet unmapped, we have already available many, sometimes all, of the varied mechanisms necessary to a true reversal of the deranged physiologic processes leading to arthritis.

In his presidential address to the American Society for Clinical

Investigation, Paul recently stated with commendable courage, "A dominant thing about some of our present notions of causative factors is that unless they fit into a modern pattern of our own liking, they are apt to be overlooked. Of late years conservative opinion does not allow anything to be really considered 'etiology' unless we can succeed in getting it into a test tube." Perhaps nowhere have these remarks more relevance than in the multi-facetted problem of arthritis.

With a general growth of interest in the physiologic deviations of the syndrome it becomes important to reaffirm that certain clinical and physiologic considerations should receive more attention.

An important lesson has been taught by study of the mild deficiency syndromes. The reciprocal factors making toward, or away from, these states do not necessarily operate separately to produce or cure the disease. Expenditure of energy, imbalance of foodstuffs, infection or minor changes in gastro-intestinal function, may be as instrumental, in the production of a deficiency syndrome, as is a true primary inadequacy.

Clinical experience usually runs ahead of precise evaluation of its components and to negative comparable influences in the field of arthritis because they do not constitute the sole cause, is to fail to see the problem whole in terms of practical therapy.

The writer believes that even in attempting to evaluate the influence of focal infection, as in the interesting article referred to earlier, the conditioning factors which make infection operative or otherwise must be equally evaluated, if the conclusions are to have any significance. To state that in a given series, removal of infection is unsuccessful may be simply to state that removal is unsuccessful under conditions such that it could hardly be expected to be otherwise. Great injustice may thus be done to the significance of removing infection if it be viewed apart from its real setting; surgically rather than biologically, so to speak. Incidentally, removal of infection is often not so complete as supposed.

Undue difficulty is apparently encountered on the part of some who treat arthritics. Perhaps one reason is not far to seek. Much recent dogma has been too strong, both pro and con. Perhaps the negative postulate is now a greater offender than the enthusiastic claims of yesterday.

The fact that faulty posture in respect to lordosis, a narrow costal angle and visceroptosis is not "the cause" of arthritis and that betterment of these handicaps does not alone "cure" all cases, does not justify zealous sceptics in discounting useful fragments of a philosophy possibly wider than their own.

Again, the fact that Raynaud's disease is not accompanied by classical arthritis does not constitute evidence that disturbances in the finer circulation bear no relation to arthritis. All clinical experience negatives such an oblique outlook.

In few syndromes is nutritional imbalance more observable than

in the arthritic. Atrophy of bone, subvitaminosis, faulty hematopoiesis, altered plasma proteins and tissue edema are common spectacles.

Some of these deviations are open to prompt amelioration; but, in general, little refinement of approach is evident in attempting to prevent or correct them.

Again, the functions of the gastro-intestinal tract present a chapter of physiology too complicated to be dismissed cavalierly. To mention only a few considerations, Ghormley *et al.*⁵ have observed recently an increased incidence of osteoporosis in elderly persons. They point out that protracted deficiencies in basic nutrition from poor dietary habits may impair the health of the adult and contribute to disabilities commonly attributed to old age. Apart from the intake of calcium, vitamin D and imbalance of the main caloric foods in the diet, the ability to absorb mineral salts from the intestinal tract grows less with age. Ivy has shown the importance of gastric function in mineral metabolism, even in puppies. The recognized decrease in gastric HCl of older persons may have consequences more significant than is generally realized. Edström⁴ recently reported a depressive secretory anomaly of the stomach in 30% of atrophic arthritics. In a review of 100 normals and 100 arthritics of both types from the Roentgen ray standpoint, Spackman has observed clear-cut anatomic and physiologic deviations in the lower gastro-intestinal tract of the arthritic groups. The writer believes that neither great type of arthritis lies wholly without the framework of these general concepts.

By the same token, dogmatic allocation of hypertrophic arthritis to age and trauma alone leaves unbridged a philosophic chasm into which many arthritics are falling. Among other evidences indicating systemic disturbance, Dandurand and Scull have recently observed reducing bodies other than glucose in the blood of hypertrophic cases in amounts significantly higher than in normal subjects.

The point of view from which the observer regards the arthritic scene has too much importance. To him who learns arthritis through bacteriology, few other phases of medicine may seem to touch it. To the pathologist, the microscope alone reveals what is worthy of notice. To the practitioner, basic considerations may seem futile since his patients await relief from pain and want it now. Like too many bands in a parade, only cacophony may result, unless each be coördinate with the others. The parade need not be so much out of step, however, as it seems to be.

Between a strong therapeutic nihilism on the one hand and wishful thinking on the other, there is a middle ground in the care of arthritics, within which many experienced students and clinicians find cause for great optimism. Successful therapy within this ground cannot be achieved by means of any alleged panacea, or, by means of such platitudes as "good hygiene, fresh air and keeping the bowels open." It can be frequently achieved, however, on the basis of a

systematic and directional attempt at readjustment of all the dislocated physiologic processes accompanying and largely characterizing the disease. This usually requires sustained study of arthritis from this angle. The lesson is not quickly learned and cannot be compressed into the narrow limits of an address. A mere titular recital of the steps involved no more equips the student than it does in major surgery.

For any one treating arthritics to lack a good working familiarity with the disease so viewed, as well as with the work of serious students in general, is to reveal a situation which this Society can properly deplore and the laity properly criticize. There is small doubt, however, that in some quarters such a situation exists today.

It is possible that the future may reveal some single factor causative of the disease. Thus Collier³ has recently observed a transmissible arthritic disease of rats, and Sabin⁷ has reported a "pleuropneumonia-like" organism comparably influential in mice.

By the same token, the future may hold some single remedial agency which will reach to or near the heart of the oak but we are not yet in possession of it. Perhaps gold will prove as valuable to the patient in his body as it has proven to be in his pockets. The somatic substrate of the arthritic subject, however, may not be so easily altered and usually needs a different approach. Biologic experience teaches increasingly that the cause of disease processes usually lies back of the firing line, so to speak. Binger well expresses this point of view: "Our attitude toward disease is changing. It is no longer satisfactorily explained as a catastrophic invasion by noxious agents, a belief handed down to us not by bacteriologists alone. . . . We know now that it requires more than the tubercle bacillus to make a man tuberculous, more than a specific antigen to produce an asthmatic attack and more than pneumococci to precipitate an attack of pneumonia. . . . There is now a growing body of evidence which leads to the belief that . . . disease, be it infectious, allergic, functional, organic or degenerative, has its developmental history in which the whole personality is involved."

Whether we like it or not, we must today face the fact that, lacking that final illumination of arthritis which is our goal, we are definitely expected in the present half light to use all such well considered measures as are available to us, or else deserve the reproaches of society. At last analysis the care of arthritics as a whole falls upon the general practitioner. He properly takes his therapeutic cue from those studying the disease and unless a reasonably wide-angled and, above all, a coördinated program be presented to him he cannot be blamed if he turns from academic negativism to the samples sent him by a drug house. To know how to utilize the components of rest; to stimulate here and sedate there; to appreciate the significance of deficiencies or surfeits, to recognize and correct them; to discover an infectious or other morbid nidus, to understand whether and when to remove it; to reëducate the patient toward his

problem; to adjust his somatic and local mechanics; in sum, to "equilibrate" the arthritic and treat him as few sufferers from other diseases are treated—this constitutes, in the opinion of the writer, at least an approach towards a specific therapy which must be experienced to be understood.

There is at the moment a real danger that in our separate quests for the cause of arthritis we are losing some perspective in the cause of arthritics. The chief purpose of this paper is, therefore, to present two objectives:

First. Avoidance of the exclusive outlook in this vexed field and the maintenance of a balanced perspective toward *all* deviations presented by the arthritic;

Second. Recognition that effective therapy often depends upon coördinating the influences of many physiologic processes, and that utilization of these influences can be achieved only by those who recognize the importance of this coördination and are sufficiently desirous of bringing it about.

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THE USE OF SULFAPYRIDINE* IN THE TREATMENT OF GONOCOCCAL URETHRITIS IN THE MALE

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THE use of sulfapyridine (2(para-amino-benzene-sulfonamido)pyridine) was first reported by Whitby¹⁰ in May, 1938, in the treatment of experimental infections in animals. Following shortly upon the reports of the drug's phenomenal clinical success in the treatment of pneumococcal pneumonia, Lloyd, Erskine and Johnson⁷ in England,

* Merck & Co., of Rahway, N. J., kindly supplied the sulfapyridine used in this study.

Durel³ in France, and later Bowie¹ reported preliminary results which suggested that sulfapyridine would prove to be at least as successful as sulfanilamide in the treatment of gonorrhea.

These results led us to a trial of the treatment of gonococcal urethritis in the male with sulfapyridine. We were early^{5,8b} impressed with its efficiency and felt justified in continuing our study with a larger number of patients.

Material. Our material consisted of 80 male patients with gonococcal urethritis observed in the Urological Out-Patient Department of the Hospital of the University of Pennsylvania. Of these, 29 were white and 51 negro ranging from 17 to 48 years. Following Pelouze^{8a} and Eisendrath and Rolnick,⁴ we have classified as acute those cases of less than 3 months' duration, as subacute those lasting between 3 and 6 months and as chronic those over 6 months' duration. There were 70 cases of acute urethritis of which 31 were anterior only and 39 antero-posterior; 6 cases of sub-acute urethritis of which 3 were anterior and 3 were antero-posterior, and 4 cases of chronic urethritis, all of which were antero-posterior urethral infections. Forty-one of the patients had had previous attacks of gonorrhea, from 1 to 7 times. When presenting themselves for treatment, 1 had inguinal adenitis, 3 had bilateral epididymitis, 1 unilateral epididymitis and 1 gonorrheal arthritis. Fifteen patients had had one or more of the following drugs in the treatment of his present infection without success: sulfanilamide, sulfanilyl-sulfanilamide, neo-protonsil and para-amino-benzene-sulphonamido-d-camphor sulfonate; 7 had had a combination of local therapy and one or more of the above mentioned drugs and 6 had had only local treatment.

Procedure. Gram negative intracellular diplococci were demonstrated by means of Gram stain of the urethral discharge in all of the patients before treatment was instituted. The patients were seen, when possible, at 2- to 3-day intervals, the urine being examined by the two-glass test. Gram stains of the urethral discharge were made frequently. A complete blood count was obtained on the day treatment was begun and was repeated in 5 to 7 days, and oftener if thought necessary. In the majority of cases blood sulfapyridine levels were taken after 4 days and again after 10 and 14 days.

Dosage. The dosage scale employed was chosen arbitrarily and adhered to routinely unless some untoward reaction occurred. This consisted of 3 gm. of sulfapyridine a day for 4 days and then 2 gm. a day for 6 to 10 days given in divided doses. Sulfapyridine was not administered continuously over more than a 2 weeks' period of time except in 1 hospitalized patient.

Criteria of Cure. The following provocative tests of cure were employed when the urine had remained clear for from 4 to 6 days following discontinuance of clinical symptoms:

1. Massage of the prostate and seminal vesicles;
2. Passage of bougies and sounds with digital stripping of the anterior portion of the urethra;
3. Consumption of alcoholic drinks;
4. Sexual intercourse with a condom;
5. One to two negative cultures* of the prostatic secretion.

* Sediment from centrifuged first portion of voided urine after prostatic massage grown on "chocolate" ascitic agar in 10% CO₂. Identification of colonies made by oxidase reaction and sugar fermentation.

Results. Of the 80 patients treated with sulfapyridine, 17 either failed to complete the course of treatment or failed to complete the tests of cure. This left 63 patients, the majority of whom were followed 2 or more months. Of the patients followed, 54 had acute urethritis, 42 (77.8%) being cured; 4 had sub-acute urethritis, all of whom were cured, and 4 had chronic urethritis, all but 1 being cured. There were followed 26 patients with anterior urethritis, 21 (80.8%) being cured, and 37 with antero-posterior urethritis of whom 29 (78.4%) were cured. In all, there were 50 patients (79.2%) who were classified as cures (Table 1).

TABLE 1.—RESULTS OF TREATMENT WITH SULFAPYRIDINE.

	No. of patients.	Cures.		No. of defaulters.	No. of failures.	Average duration of discharge of cures, days.
		No.	%.			
Total series	80	50	79.2	17 (21%)	13	2.77
Acute urethritis	70	42	77.8	16	12	2.93
Anterior	31	18	78.3	8	5	3.42
Posterior	39	24	77.4	8	7	2.5
Subacute urethritis	6	5	100.0	1	0	1.8
Anterior	3	3	100.0	2.3
Posterior	3	2	100.0	1.0
Chronic urethritis	4	3	75.0	..	1	2.3
Posterior	4	3	75.0	..	1	2.3
Anterior urethritis	34	21	80.8	8	5	3.3
Posterior urethritis	46	29	78.4	9	8	2.4

The average duration of urethral discharge in the cured patients after onset of therapy was 2.77 days. This, of course, represents a remarkable advance over the older forms of treatment with sedation and local therapy, with which, in the experience of this Department, 10 days to 2 weeks almost invariably elapsed before the same improvement occurred. In the cases of acute urethritis, the average duration of discharge was 2.93 days; in the subacute cases, 1.8 days; the chronic cases, 2.3 days (Table 1).

It is interesting to note that there were 19 patients in the series who had been previously treated with, and resistant to, one or more of the following drugs: sulfanilamide, benzyl sulfanilamide, sulfanilyl-sulfanilamide, neo-prontosil and p-amino-benzene-sulfonamido-d-camphor sulfonate. Of these, 13 (68.4%) were cured with sulfapyridine (Table 2).

TABLE 2.—SULFANILAMIDE GROUP RESISTANT CASES.

	No. of patients.	Cures with sulfapyridine.	
		No.	%.
Total series	19	13	68.4
Acute urethritis	13	8	61.0
Subacute urethritis	2	2	100.0
Chronic urethritis	4	3	75.0

Complications. During the course of treatment there occurred 1 case of unilateral epididymitis, 1 of bilateral epididymitis and 2 of gonorrheal arthritis. All of these patients were treatment failures. Of particular interest, we believe, are the 2 cases of arthritis, a greater ratio than we have seen in routine or previous chemotherapeutic treatment of gonorrhea. Both of these were later cured, 1 following treatment with the Kettering hypertherm* and the other following a second course of sulfapyridine.

The patients with inguinal adenitis, unilateral epididymitis and gonorrheal arthritis present before sulfapyridine therapy were all cured. Of the 3 patients with bilateral epididymitis only 1 was cured. In the remaining 2 cases the onset of toxic reactions necessitated withdrawal of the drug before a complete course of the drug had been given.

Toxicity. Forty-five patients (56.2%) had one or more toxic reactions, of which 11 (13.9%) were classified as severe. Among the 50 patients classified as cured, 27 (54%) had some toxic reaction, while in the group of 13 failures a higher incidence was noted, 10 (76.9%) showing untoward reactions (Table 3).

TABLE 3.—TOXIC REACTIONS FROM SULFAPYRIDINE.

	No. of patients.	Total reactions.		Severe reactions.	
		No.	%.	No.	%.
Total series	80	45	56.2	11	13.9
Cures	50	27	54.0	4	8.0
Acute urethritis	42	24	57.1	3	7.3
Subacute urethritis	5	3	60.0	1	20.0
Chronic urethritis	3	0	..	0	
Failures	13	10	76.9	6	46.0
Defaulters	17	8	47.0	0	

The mild toxic reactions following administration of sulfapyridine were headache, nausea, apathy, weakness, dizziness, nervousness, substernal discomfort, pruritus and myalgia. The more severe reactions seen were pyrexia, vomiting, morbiliform rash, generalized hyperemia, polyarthritis, chills, and leukopenia (Table 4). Because these patients were ambulatory, it was thought advisable in the presence of the more severe reactions to stop the administration of sulfapyridine.

There was a general tendency toward leukopenia noted in the majority of cases. In 2 patients the white blood count during treatment was reported to be 3000 and the drug was stopped, although in neither case was there evidence of agranulocytosis. It may be well to note that we have observed no gross hematuria or symptoms of renal colic during the administration of the sulfapyridine in the above prescribed dosage. In 7 of our patients there was a definite pyrexia. This is a higher incidence than was reported by one of us⁹ in a series of 400 cases of pneumococcal pneumonia treated with

* Courtesy of Dr. F. Fetter, Philadelphia General Hospital.

sulfapyridine, in which the diagnosis of drug fever was only made twice. This may be due to the fact that the gonorrheal cases were ambulatory and although given smaller dosage, were treated for a longer time.

TABLE 4.—VARIETY OF TOXIC REACTIONS.

	No.
Headache	35
Nausea	23
Apathy	9
Weakness	7
Pyrexia	7
Dizziness	5
Vomiting	4
Morbiliiform rash	3
Nervousness	3
Insomnia	2
Confusion	1
Chills	2
Leukopenia	2
Hyperemia	1
Polyarthritis and edema	1
Pruritis	2
Substernal discomfort	2
Myalgia	1

It is interesting to note that 51.1% of the patients who suffered mild reactions and 70% of those developing the more severe symptoms of toxicity had had administered to them previously one or more of the sulfanilamide group of drugs above mentioned (Table 5). All of the toxic reactions rapidly subsided on withdrawal of the drug and a large fluid intake by mouth.

TABLE 5.—PATIENTS WITH TOXIC REACTIONS WHO HAD PREVIOUS TREATMENT WITH SULFANILAMIDE GROUP DRUGS.

	No. of patients.	Percentage of patients.
Among all patients showing reactions	22	51.1
Among patients showing severe reactions	7	70.0

Blood Sulfapyridine Level. We have found no significant difference between the average blood levels of sulfapyridine in the cures and failures, the former being 2.8 mg. per 100 cc. of blood and the latter 2.3 mg. Although those patients with subacute urethritis had an average blood sulfapyridine level of 5.1 mg. per 100 cc. the percentage of patients having untoward reactions is not much greater than that of the patients with acute urethritis whose average blood sulfapyridine level was 2.5 mg. The patients with chronic urethritis, who showed no toxicity, had an average blood sulfapyridine level of 2.6 mg. per 100 cc. (Table 3). Nor was there found a significant variation between the average blood sulfapyridine levels and those patients with mild reactions which was 3.1 mg. per 100 cc., and those with severe reactions which was 3.5 mg. The only excep-

tion to this was 1 patient with a blood sulfapyridine level of 9.3 mg. per 100 cc., who developed a diffuse morbiliform rash and leukopenia.

Discussion of Failures. Among the patients classed as failures were 6 in whom the administration of sulfapyridine was stopped because of severe reactions before a complete course of the drug had been taken. Of these, 1 was cured by a second course of sulfapyridine without the reappearance of toxicity, but does not appear in our statistics as a cure. Four patients of this group were later cured following a short regimen of local therapy, the total time involved being less than might be expected if local therapy alone had been used. The remaining patient was a truant and still had gonorrhea when last seen.

One patient was not only a failure after prolonged treatment with sulfapyridine, but developed gonorrheal arthritis while under treatment, he being the one exception to the 2 weeks' rule of therapy. He was later cured by hyperthermia. The other patient who developed gonorrheal arthritis and who was a failure on one course of sulfapyridine was cured by a second course with a maximum dose of of 2 gm. per day. There were 2 patients in whom there were no apparent benefits seen but who were cured subsequently with a short course of local therapy. Another showed improvement but defaulted after sulfapyridine was stopped.

The remaining 2 patients who were failures illustrate the value of the complete schedule of the tests of cure. One passed all of the tests of cure except the culture which was returned as positive 1 month after cessation of therapy. The other patient, following a negative first culture, had a recurrent slight morning discharge after the passage of bougies and a second culture was positive 5 weeks after the cessation of therapy. In neither of these cases was there obtained a history of re-exposure to gonorrhea.

Discussion of Defaulters. A review of those patients who either failed to complete their course of treatment or failed to complete the tests of cure reveals some interesting points. In this category are 17 (21%) patients of whom 12 were negro and 5 were white. In out-patient department work of this character a certain number of patients default. This is particularly true at the present time, when so many transients are wandering from city to city in search of work. Three patients visited the clinic once only, 3 had only two visits and no surmises can be drawn about them. One patient completed almost his entire course of therapy without much improvement and was a probable failure. Another also had completed almost the entire prescribed course but his urine which had become clear was hazy on his last visit. However, the remaining 9 patients were all probable cures, their urine having been clear for from 3 to 10 days. One of these had had all of the tests of cure but did not return for follow up, and another had had the passage of bougies without

recurrence of discharge or pus in the urine when last seen. Eliminating the patients who were seen on only 1 or 2 occasions, there was then 81.8% of probable cures in this group of patients who defaulted.

TABLE 6.—COMPARATIVE RESULTS IN THE TREATMENT OF GONORRHEAL URETHRITIS IN THE MALE WITH SULFAPYRIDINE.

	Dosage of sulfapyridine.	Local treat- ment.	No. of male pa- tients.	Tox- icity, %.	Disap- pearance of dis- charge after treat- ment.	Successful results, %.
McGregor-Robertson, J. G.: Lan- cet, 2, 1463, 1938	19 gm. in 7 days	With	100	45.0	4.5	96.0
	21 gm. in 7 days	Without	101	..	3.3	80.0
Lloyd, V. E., Erskine, D., and John- son, A. G.: Ibid., p. 1160	22.5 gm. in 10 days	With	108	22.0	3.9	85.0
Prebble, E. E.: Ibid., p. 1163	15-60 gm. in 5-12 days	Without	25	5.6		48.0
		With	40			62.5
Bowie, F. J. T., Anderson, T. E., Dawson, A., and Mackay, J. F.: Brit. Med. J., 1, 711, 1939	Variable; average, 3 gm. per day for 4-5 days, then 1.5 gm. per day for 3-4 days	Without	73	37.0 on aver. dosage		93.0+
		With	24			
Durel, P.: Presse méd., 46, 1571, 1938	18 gm. in 9 days	Without	73			Acute, 80 Prolonged 70
Leroy, J.: Ann. d. mal. ven., 33, 729, 1938	3 gm. per day for 10 days or less	Without	22	30.0		81.8
Batchelor, R. C. L., Lees, R., Mur- rell, M., and Braine, G. I. H.: Brit. Med. J., 2, 1142, 1938	3 gm. per day for 5 days then reduced for 7 to 9 days	Without	79	25.3	4.0+	92.4
Girard, Andorino et Jaubert: Ann. d. mal. ven., 34, 83, 1939	18 gm. in 9 days	Without	20	Slight		100.0
Marinkovitch, R.: Brit. Med. J., 1, 317, 1939	42 gm. in 21 days	With	50	8.0		86.0
Reyn, A.: Ugesk. f. læger., 101, 466, 1939	12.5 gm. in 8-14 days	Without	30	7.0		Acute, 87.0
			10			Chronic, 90.0
Johnson, S. H., Leberman, P., and Pepper, D. S.	3 gm. per day for 4 days, then 2 gm. per day for 6-10 days	Without	76	56.2	2.77	80.3

Comment. A survey of the available literature on the treatment of gonorrhea with sulfapyridine reveals an almost universal opinion that the results obtained with sulfapyridine surpass those obtained with sulfanilamide. This coincides with the results seen in this clinic by 2 or us⁶ when under the same conditions as the present study we had only 40.6% of cures with sulfanilamide. None of the four other sulfanilamide derivatives that have been used in this clinic in the treatment of gonorrhea in the male have given as good results as we have seen with the use of sulfapyridine. The results obtained in series of patients that are comparable to ours, by other

writers (Table 6) are in general somewhat better. However, some of the statistical cures are quoted as successful results and the criteria of cure are not always given. If we include the 2 patients in our series who were failures with one course of sulfapyridine and who were cured with a second course of the drug, and the 9 defaulters who were probable cures, we obtained 80.3% of successful results. We have found sulfapyridine to be efficacious in the treatment of gonorrhea that has been resistant to previous therapy with other drugs of the sulfanilamide group. Cokkinis and McElligott² advise delay in administering sulfapyridine until the second week of the disease; we, however, have seen no rationale in this delay both from the ultimate results and from the patient's viewpoint. Delay is dangerous from a public health standpoint in the early highly infectious period, it increases the anxiety of the patient because of persistence of symptoms, it brings close the danger period of complications and increases the likelihood of the patients defaulting. Although our dosage scale was approximately average in comparison to that of other authors quoted (Table 6), the incidence of toxicity in our series is higher than in any series we have noted. This may be due to the fact that a particular effort was made each visit, to inquire specifically if any untoward reactions had occurred. The rather high percentage of toxicity (56.2%) is, however, not significantly different from the 55% of untoward reactions that we reported⁶ in a series of male patients with gonorrhea treated with sulfanilamide. None of the toxic reactions have resulted in impairment of the patient's health. We do not think that a dose higher than 3 gm. a day is necessary or justified in an ambulatory patient, and this should be reduced to 2 gm. a day or less if toxic reactions are prominent. If sulfapyridine is going to be effective, it will almost invariably be so within the first week of treatment, and we therefore feel that the primary course should not be prolonged over a period of 2 weeks. In view of the two favorable results following a subsequent course of the drug, it is thought that the use of repeated courses of sulfapyridine is worthy of further trial. From our experience with blood sulfapyridine levels in this series of patients, we have decided that they are of no value as we have not been able to correlate the blood level with either the incidence of toxic reaction or the clinical response to the drug.

Summary. 1. Sixty-three of 80 male patients with gonorrheal urethritis, treated with sulfapyridine, were adequately followed.

2. Of these 63 patients, 50 (79.2%) passed all the tests of cure, the average duration of discharge in these cases being 2.77 days.

3. The dosage schedule was 3 gm. of sulfapyridine a day for 4 days, then 2 gm. a day for 6 to 10 days.

4. In a group of 19 patients resistant to previous treatment with a sulfanilamide derivative, 68.4% were cures with sulfapyridine thereafter.

5. Forty-five patients (56.2%) had one or more toxic reactions.

6. Blood sulfapyridine levels were of no significance in prophesying reactions or cures.

Conclusion. In our experience, sulfapyridine has been the most efficient sulfanilamide derivative in the treatment of gonococcal urethritis in the male.

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THE ELIMINATION OF THE EFFECT OF THE CHEMICAL MEDIATOR OF RENAL HYPERTENSION.* †

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HYPERTENSION of renal ischemic origin, according to our previous results,^{7,13,14} appears to depend upon the ratio of ischemic to normal kidney substance. For example, the removal of the normal kidney in normotensive dogs with unilateral renal ischemia results in a reappearance or intensification of the hypertension. These observations might have been due to an increase in the load of the remaining kidney aggravating its relative ischemia rather than to the removal of any counteraction on the part of the normal kidney. We have, therefore, subjected this concept to further study by noting whether or not the presence of a normal kidney had any effect on the dissipation of the hypertension following removal of the ischemic kidney.

Method. For this purpose, the results of two types of nephrectomies in hypertensive animals were compared: *a*, when the ischemic kidney responsible for the hypertension was removed leaving the normal kidney *in situ*; and, *b*, when a total nephrectomy was done. As controls, the blood pressure changes in normotensive animals were followed after unilateral or bilateral nephrectomy.

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All blood pressure determinations were made without anesthesia using the Hamilton needle manometer technique,¹⁰ which gives accurate systolic and diastolic pressures. All the operations were done aseptically, the renal clamps being applied under nembutal anesthesia, and the nephrectomies under ether. Only trained dogs were used. The period of training was considered completed when the diastolic blood pressure on at least three successive readings was found to be constant within ± 5 mm. Hg. After a satisfactory control period was obtained, these animals were subjected to unilateral or bilateral renal ischemia using the Goldblatt technique.⁹ Some days after hypertension had developed, the appropriate nephrectomy was done and hourly determinations of blood pressure values were made to determine how soon the normal blood pressure was reached. The time selected as the end point of the hypertensive period was that when the diastolic pressure first reached within 5 mm. Hg of the normal control pressure level. Zero time was considered to be the time during the operation when the blood supply of the kidney to be removed was occluded. In this regard, we have found that the systolic pressure is much more variable than the diastolic, especially with heart rate changes, and is therefore unsuitable for studies such as ours. This criticism also holds in the case of mean pressure which is affected by the systolic pressure. We have relied upon the diastolic pressure in our analysis since we have found this a more satisfactory criterion.

Discussion of Results. The lag in the return of the arterial pressure to normal following removal of the ischemic kidney is shown in Figures 1 and 2. The former shows the results (range and mean) when a normal kidney was left *in situ*, the latter, when no kidney remained. A typical experiment with both types of nephrectomy, is shown in Figure 3. It is apparent from these figures that a definite difference exists in the time at which hypertension disappears following removal of the ischemic kidney, depending on whether or not a normal kidney is left *in situ*. In the 6 experiments in which the ischemic kidney was removed and a normal kidney left intact, the hypertension disappeared and the normal pressure level was reached in 6, 6, 4, $4\frac{1}{2}$, $3\frac{1}{2}$ and $4\frac{1}{2}$ hours respectively, an average of 5 hours. In these animals, the ischemia had been induced by renal clamping 16, 5, 28, 10, 10 and 18 days respectively prior to the nephrectomy.

In the 7 experiments in which the remaining kidney or both kidneys were removed (total nephrectomy) in hypertensive dogs, the hypertension following the operation lasted longer; the blood pressure in these dogs remained above the normal control level for $50+$, $10\frac{1}{2}+$, between $12\frac{1}{2}$ and 21, 9, 13, 40 and 15 hours respectively. In these animals, the renal clamping leading to hypertension was done 116, 27, 11, 24, 2, 13 and 2 days respectively prior to the nephrectomy. Thus, the presence of a normal kidney reduced the duration of the hypertension following removal of the ischemic kidney, and this occurred despite the fact that in the absence of both kidneys, the animals were subject to the depressor action which accompanies the development of uremia. This difference is not related to the duration of the hypertension previous to nephrec-

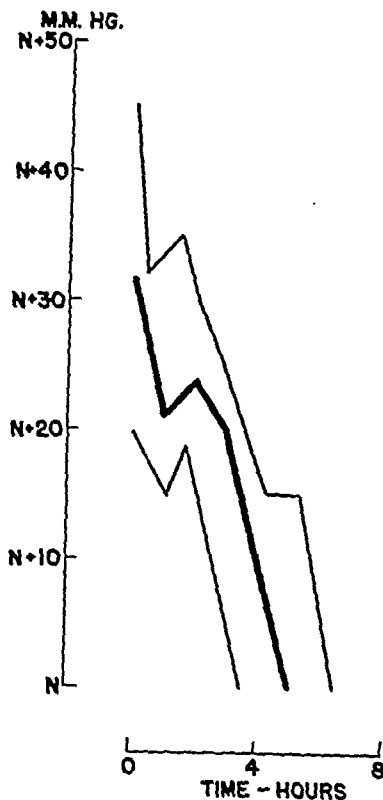


FIG. 1.—The rate of dissipation of hypertension in 6 experiments following removal of the ischemic kidney leaving a normal kidney *in situ*. Zero time is the time during the operation when the blood supply to the kidney(s) to be removed is occluded, ordinates show the diastolic pressure readings above the control level (*N*) in mm. Hg. The light lines show the range and the heavy line shows the mean diastolic pressures. Discussed in text.

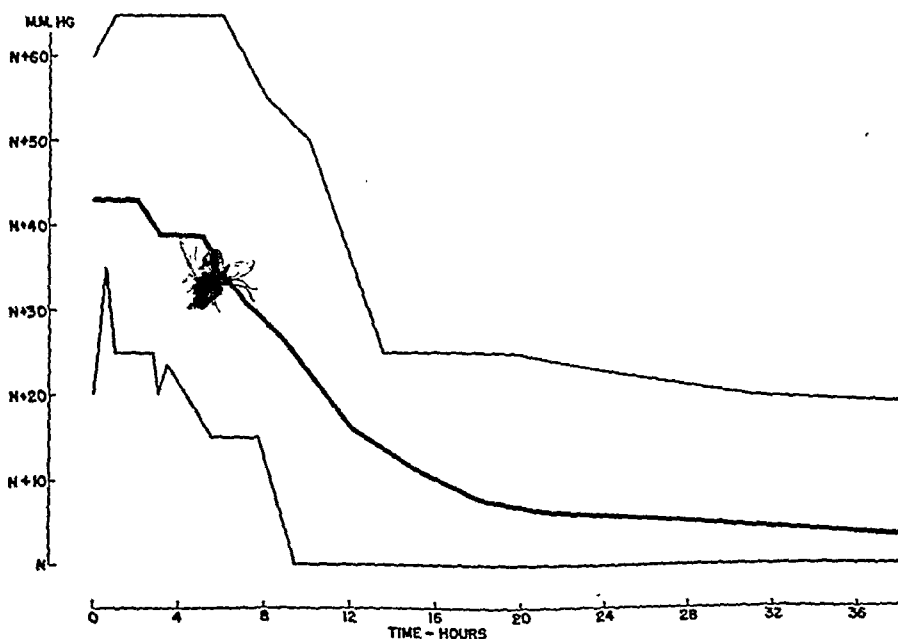


FIG. 2.—The rate of dissipation of hypertension in 7 experiments following total nephrectomy. Conventions as in Figure 1. Discussed in text.

tomy as this duration was of the same order in both groups. On the average, the blood pressure remained above the normal control

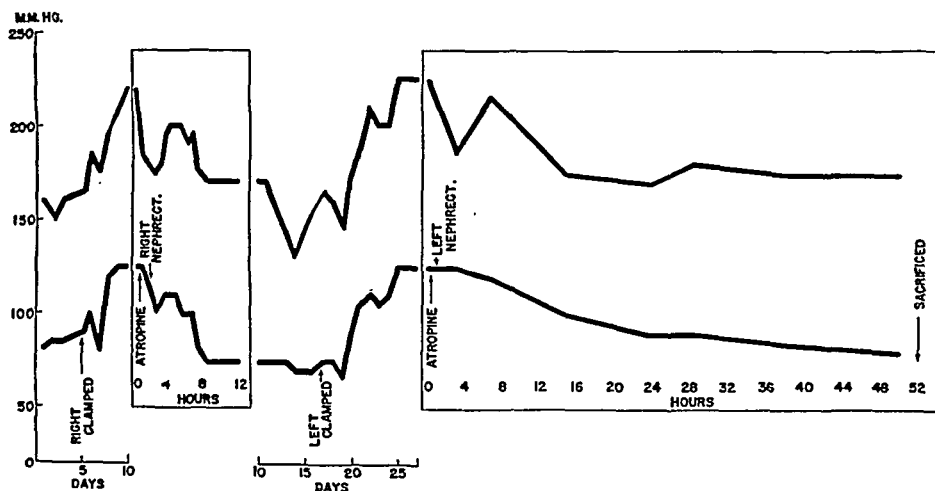


FIG. 3.—Complete protocol of a single experiment typical of all to show difference in rate of dissipation of hypertension, depending on whether or not a normal kidney was left *in situ*. Lower line is diastolic, upper, systolic blood pressure obtained from femoral artery. Note that in the frames the time scale is changed to hours instead of days. Indicated on chart are time when renal arteries were clamped and of right and left nephrectomies.

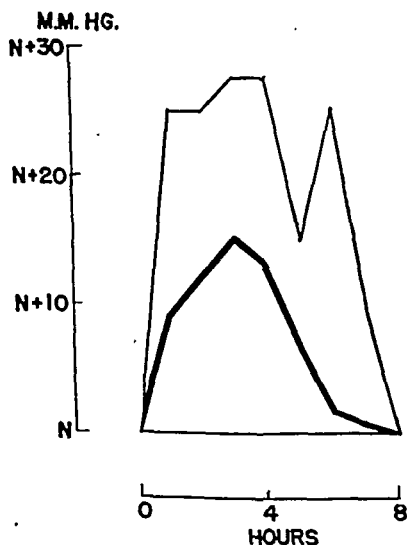


FIG. 4.—The development of a transitory neurogenic hypertension following unilateral or bilateral nephrectomy in 14 normotensive dogs. Conventions as in Figure 1. Discussed in text

level for about 28 hours after total nephrectomy, roughly 5 times longer than when a normal kidney was left in place.

It is possible that when a normal kidney remained *in situ* the lag

might have been even less than we found, since a transitory post-operative hypertension lasting about 6 hours was frequently found in normotensive animals subjected to unilateral or bilateral nephrectomy (cf. 13). Our experience on this point to date with 8 unilateral and 6 bilateral nephrectomies in normotensive dogs is summarized in Figure 4. Evidence for the presence of this complication is shown in the hump in the curves of Figure 1.

Our results are not in accord with those reported by Dicker,⁵ but the significance of his results may be vitiated by the fact that he apparently took only single daily pressure readings and utilized mean pressure variations. Furthermore, the results of Blalock and Levy and of Verney and Vogt¹⁸ are not in accord with his as regards the persistence of the hypertension. Goldblatt's^{8a} data are not detailed on this point.

While inspection of the data of Blalock and Levy² show changes which accord with ours, the sharp differentiation which we obtained is not shown in their data. The difference between our results and theirs cannot be ascribed to the general anesthesia we used during the nephrectomy operation, since we have found that ether anesthesia in normotensive dogs subjected to a mock operation does not alter the blood pressure in the postoperative period with which we are concerned.¹³ It must be due to the use of the more variable mean pressure in their experiments.

Interpretation of Results. It is evident that our present results indicate that the presence and intensity of hypertension is dependent upon the ratio:

$$\frac{\text{Amount of ischemic kidney tissue}}{\text{Amount of normal kidney tissue}}$$

This is in accord with our previous data and is supported by the recent work of Fasciolo, Houssay and Taquini,⁶ who showed that hypertension following homotransplantation of ischemic kidney is more intense in the dog previously subjected to complete nephrectomy than in the normal animal.

Our results give added weight to the thesis that hypertension due to renal ischemia is mediated by a humoral mechanism. They indicate that the chemical mediator of renal hypertension is rapidly destroyed, neutralized or otherwise eliminated when normal kidney tissue remains in the animal. In the absence of normal renal tissue, however, this process cannot occur at a rapid rate. The rapid fall in blood pressure on removal of the ischemic kidney when a normal kidney is left *in situ* leads us to the view that an equilibrium in production, on the one hand, and neutralization, destruction or elimination of the chemical mediator, on the other, has been established during the maintenance of the hypertension. Removal of the source of the chemical mediator, the ischemic kidney, upsets the equilibrium and results in a rapid elimination of the effects of the substance.

The difference in the persistence of hypertension favors the view that renin is somehow related to renal hypertension since Tigerstedt and Bergman¹⁷ showed in work since confirmed that the injection of an extract of the kidney (renin) caused a more pronounced rise in blood pressure in nephrectomized than in normal rabbits. Our results further indicate that substances which are rapidly destroyed by the extrarenal tissues can be eliminated as possible pressor factors in this form of hypertension.

Our results with nephrectomy are in line with previous work^{5,8b,9,12} in pointing to the fact that hypertension of renal ischemic origin is not due to the retention of products of tissue activity in the absence of renal excretion. However, this does not rule out the possibility that the hypertension may be due to the retention of such products of normal or ischemic kidney activity, for in complete nephrectomy, we not only remove the excretory function, but also the metabolic processes peculiar to the kidney.

The reversibility of the hypertension of short standing present in our experiments indicates that no irreversible vascular changes had yet been produced, otherwise the effects of the chemical mediator of renal hypertension would not have been so quickly eliminated. Whether a similar reversibility exists in long-standing hypertension demands further investigation.

Analysis of our experiments indicates that the maintenance of the blood pressure of the dog at a normal level does not require the presence of the kidneys. By contrast the hypertensive level following renal ischemia appears to involve the kidneys not only in its creation and maintenance, but also in its elimination. This difference in the normotensive and hypertensive mechanisms is shown in our bilaterally nephrectomized hypertensive dogs by the fact that after the blood pressure had returned to the normal diastolic level, it was maintained there until shortly before death. This sharp differentiation between the two stages in blood pressure fall points to the independent origin of the normotensive and hypertensive states. This is further supported by the fact that in normotensive dogs complete nephrectomy causes only the second preagonal fall. These facts apply, of course, only if shock and early uremia are ruled out.

These results have a bearing on clinical studies. Twenty years ago O'Connor¹⁶ reported that the drainage of the bladder by suprapubic cystotomy in cases of urinary retention following prostatic obstruction caused an appreciable drop in blood pressure within 24 hours in 41 out of 55 cases. The greater drops occurred in cases with marked hypertension. This observation has been subsequently confirmed. Since a number of investigators^{5,11,12} have found no essential differences in hypertension due to experimental occlusion of the ureter, extreme distention of the bladder and the experimental Goldblatt variety, it is easy to assume that these hypertensions are

due to the same mechanism: renal ischemia. In relieving the bladder distention, therefore, the renal ischemia was presumably relieved and the kidneys then caused the prompt drop in blood pressure just as occurs in the dog when the ischemic kidney is removed and the normal kidney is left *in situ*.

Actual removal of the ischemic kidney in human beings has been recently reported. Butler⁴ has reported a case in which removal of a pyuric kidney resulted in a return to normal pressure within one day. Barker and Waltman¹ have reported a prompt return of pressure to normal in several cases following removal of a hydro-nephrotic kidney. Leadbetter and Burkland¹⁵ noted an "immediate" decline in both systolic and diastolic pressures following removal of an ectopic ischemic kidney having its main renal artery partly occluded. Boyd and Lewis³ noted that the pressure fell "immediately" to normal after removing an infarcted kidney. Unfortunately, the hourly changes in blood pressure in these cases are not given. It would be valuable to determine whether a neuro-genic rise occurs immediately after nephrectomy in man (there was such a rise in one of Barker's cases 3 hours postoperatively). It may also be of value to determine whether the time course in such patients compares with that in the experimental animal. In view of our results, it is not impossible that the time course of the return of the pressure to normal levels will help to indicate whether or not the remaining kidney is severely damaged.

Summary. 1. Removal of the ischemic kidney in hypertensive dogs with a normal kidney remaining *in situ* results in a return to normotensive levels within 6 hours. The time period for this return might have been prolonged because of interference by the fleeting neurogenic hypertension which often follows nephrectomy.

2. Removal of the ischemic kidney in hypertensive dogs with no kidney remaining results in a considerably slower return to the normal pressure levels, averaging in our series five times that found when a normal kidney was left *in situ*.

3. These results suggest that the chemical mediator of hypertension due to renal ischemia is destroyed, neutralized or otherwise eliminated at a rapid rate only in the presence of normal kidney tissue.

4. Our results indicate that normotension is independent of renal action, while renal hypertension depends upon the kidney for its genesis, continuation and elimination.

We are indebted to Miss L. Friedberg for her assistance in carrying out these experiments.

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THE RESPONSE IN BLOOD PRESSURE OF HYPERTENSIVE PATIENTS TO ACETYL-BETA-METHYLCHOLINE.*

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THE search for the causes of arterial hypertension in man has led to the point where it may be said that high blood pressure is the result of an increased peripheral vascular tone.^{16,17,20a} The causes of the increased vascular tone are still uncertain. The sympathetic vasoconstrictor nerves have been relegated to only a contributory rôle. Search for humoral pressor substances is yet in progress and has received new impetus from a method of creating an experimental renal hypertension in animals.

There are those who already speak of an "intrinsic hypertonus of the blood-vessels," independent of any of the known mechanisms for the regulation of vascular tone. However, it is logical to assume that before investigators can speak with conviction of an intrinsic hypertonus of the blood-vessels, they must make certain that all the physiologic mechanisms contributing to the regulation of vascular tone can be exonerated as a cause of hypertension.

In this regard, we question whether the vasodilator mechanisms have been thoroughly investigated in relation to the possibility that a failing vasodilator mechanism might be a factor in the production of arterial hypertension.

The physiologic vasodilator substances of recognized importance are the metabolites of muscle contraction, histamine, and acetylcholine. It has been found that the blood-vessels of hypertensive patients respond normally to the action of the metabolites that accumulate during a period of circulatory arrest,^{16,17} so that there

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seems to be no reason to suspect a causal relationship of these metabolites to hypertension. Likewise, hypertensive subjects have been reported to exhibit normal vascular reactions to the subcutaneous administration of histamine.¹⁶ A comparison of the vascular reactions of hypertensive and normal individuals to acetylcholine has not been reported.

The physiologic importance of acetylcholine has only in the past decade begun to be appreciated in its rôle of a chemical transmitter of nerve impulses.^{1,15} It is now believed that nerve impulses, passing over certain nerves, cause the release at those nerve-endings of acetylcholine. It has been found that a single nerve impulse causes the release of a definite quantity of acetylcholine⁶ and it is assumed that variations in the tonic effect of the nerve upon its effector organ are accomplished by changes in the frequency of the nerve impulses travelling over the nerve and the alterations thus produced in the concentration of acetylcholine at the nerve-endings. The concentration of acetylcholine at the nerve-endings is also influenced by an esterase within the tissue fluids which constantly destroys acetylcholine. It is further known that the effect of the nerve impulse is due solely to the acetylcholine present at the nerve-endings, and that this effect can be mimicked by the administration of acetylcholine.^{1,10,11} Experimental evidence supports the belief that administered acetylcholine affects only those effector cells that are innervated by the so-called cholinergic nerves.

Generally speaking, the autonomic nervous system exerts its control over vital processes of the body by means of dual mechanisms, one having an inhibitory function and the other having an excitatory function. The autonomic control over the cardiovascular system is no exception. The excitatory influence is mediated by the sympathetic vasoconstrictor and cardiac accelerator nerves, which liberate at their nerve-endings an adrenalin-like substance called "sympathin E."² The inhibitory influence is exerted by the nerves which liberate acetylcholine. This dual control over the heart rate has been investigated in detail by Rosenblueth and Simeone.¹⁹ However, the possibility of the existence of a similar dual nervous control over peripheral vascular tone is much less evident. Vasodilator nerves have usually been regarded as unimportant, chiefly because it is known that nearly all the measurable vascular reactions to cooling or warming the body, to pain and to other external stimuli, are mediated largely through the sympathetic vasoconstrictor nerves. However, it seems possible that vasodilator nerves may exert a restraining influence on vascular reactions, and that they may help to maintain a basal vascular tone upon which the activity of the sympathetic vasoconstrictor nerves are superimposed.

It is important to note that vasodilator nerves are distributed throughout the body. Of particular interest are those in the posterior spinal nerve roots because they are unaffected by sympathectomy;

and in the experimental animal they are known to be in constant tone and also to possess central reflex connections.^{8,18} Their presence in man has been demonstrated⁷ but there is little direct evidence relating to the extent of their influence on peripheral vascular tone. Evidence favors the opinion that they are cholinergic.^{21a,b} This does not mean that atropine abolishes their effect, because oddly enough, it does not.¹⁰ However, the effect of stimulating the vasodilator nerves in the posterior roots is enhanced by eserine.^{21b}

On the basis of these considerations, we wished to administer acetylcholine to hypertensive patients and to compare the responses in blood pressure to those of normal controls. We reasoned that if in hypertensive individuals the blood-vessels were insensitive to acetylcholine, or were protected from it by some atropine-like substance, we might expect to obtain a subnormal response. We further reasoned that a hyper-response on the part of hypertensive individuals might be the result of a subnormal concentration of acetylcholine around the peripheral blood-vessels, because it is an established fact that after the section and degeneration of the cholinergic nerve supply to a part of the body, that part exhibits a marked sensitivity to the effects of acetylcholine.^{1,4,5} Furthermore, if the blood-vessels of hypertensive individuals do respond excessively to acetylcholine, it seems reasonable to postulate that a diminished function of the cholinergic vasodilator nerves is present; otherwise, we should expect a marked peripheral vasodilation to obtain in the hypertensive subject, whereas we believe that quite the opposite condition, a generalized peripheral vasoconstriction, exists.

In conducting our studies we substituted for acetylcholine one of its derivatives, acetyl-beta-methylcholine (mecholyl, Merck).^{*} It seemed desirable to make this substitution because the latter is more stable both in solution and in the body than the former, permitting the investigator to measure more accurately the minor effects resulting from the administration of small doses of the drug. This substitution seemed permissible on the ground that the peripheral action of both drugs is qualitatively the same in the cases of both experimental animals and normal^{3,20b} human beings, and on the grounds that the effects of both drugs are similarly altered by the presence of atropine or eserine.^{13,14} It would seem, therefore, that the action of both drugs is dependent upon the same physiologic mechanism, and that we might expect that an individual would react similarly to either drug.

We administered acetyl-beta-methylcholine in 2.5 mg. doses subcutaneously to normal individuals (Table 1) and found that it produced little or no decrease in blood pressure. Other investigators have reported that dosages up to 5 mg. usually produce a slight

* We are indebted to Merck & Co. for the acetyl-beta-methylcholine (mecholyl) used in making these observations.

TABLE 1.—NORMAL INDIVIDUALS: RESPONSE TO MECHOLYL, 2.5 MG., SUBCUTANEOUSLY.

Case.	Sex.	Age, Yrs.	Resting B. P.	Lowest B. P. after mecholyt.	Percentile decrease.*	
					Sys- tolic.	Dias- tolic.
41	F	28	104/58	94/56	9.6	3.4
42	M	29	100/72	92/66	8.0	8.3
43	M	28	100/68	94/64	6.0	5.9
44	F	28	100/64	88/60	12.0	6.2
45	M	30	116/78	110/76	5.2	2.6
46	M	29	100/74	96/68	4.0	8.1
47	F	25	102/56	96/54	5.9	3.6
48	M	30	120/82	116/80	3.3	2.4

* Pressure after mecholyt compared with resting pressure.

TABLE 2.—HYPERTENSIVE PATIENTS: RESPONSE TO MECHOLYL, 2.5 MG., SUBCUTANEOUSLY.

Diffuse Arterial Disease, Group 1.

Case.	Sex.	Age, Yrs.	Weight, pounds.	B. P. in consultant's office.	Resting B. P. in hospital.	Lowest B. P. after mecholyt.	Percentile decrease.*	
							Sys- tolic.	Dias- tolic.
33	M	25	149	130/78	130/66	90/40	30.8	39.4

Diffuse Arterial Disease, Group 2.

1	F	65	168	230/130	156/89	128/70	17.9	21.3
2	F	40	132	180/110	174/112	134/74	23.0	35.5
3	F	42	148	210/110	180/108	132/78	26.6	27.7
5	F	49	125	230/130	160/98	142/84	12.5	14.3
6	F	59	131	170/100	110/60	86/48	21.8	20.0
7	F	41	118	200/130	164/106	120/76	26.8	24.0
9	M	35	155	164/90	146/80	124/64	15.1	20.0
10	F	38	118	190/120	180/118	140/88	22.2	24.1
11	M	41	165	216/140	158/108	130/84	17.6	22.2
15	F	54	140	176/104	138/80	110/62	20.3	22.5
16	F	46	139	220/110	170/100	144/74	15.3	26.0
19	M	33	162	210/130	156/112	138/80	11.5	27.3
22	F	31	105	220/120	174/110	162/90	7.0	18.2
24†	M	38	193	180/120	170/108	162/110		
25	F	60	155	214/120	140/80	130/68	7.1	15.0
27	M	45	154	165/100	130/84	104/74	20.0	11.9
29	F	60	141	220/114	174/86	130/68	25.4	20.9
30	F	36	135	220/120	144/104	124/64	13.9	38.4
31	F	41	154	168/114	120/90	104/74	13.3	18.8

Diffuse Arterial Disease, Group 3.

4	M	27	148	200/145	200/140	166/114	17.0	18.6
8	M	54	167	210/130	180/120	160/100	11.1	15.3
12	M	36	206	205/130	184/146	160/116	13.0	20.5
18	F	30	126	190/120	158/120	120/90	24.1	25.0
17	M	40	134	208/130	190/118	174/90	8.4	25.0
34	F	34	120	216/140	194/132	146/92	27.4	30.3

Chronic Glomerulonephritis.

13	M	24	140	160/100	168/106	128/64	23.8	37.4
14	M	46	203	170/110	128/88	110/72	14.1	18.2
20	M	63	176	192/104	164/96	134/80	18.3	16.6
21	F	19	115	144/90	134/62	116/38	13.4	38.7
26	M	56	150	190/100	154/80	136/68	11.7	15.0
28	M	28	154/96	130/64	15.6	33.3
32	M	28	140	190/126	186/126	166/100	10.8	20.6

* Pressure after mecholyt compared with resting pressure.

† See text.

increase in the blood pressure of the normal human being.¹³ In either case, the effect is slight.

In the same manner, we administered acetyl-beta-methylcholine to hypertensive patients (Table 2). These were all patients who had been hospitalized for study. Their diagnoses included Groups 1, 2, and 3 of essential hypertension,¹² and hypertension associated with chronic nephritis and pyelonephritis. The results of this comparison are given in Tables 1 and 2. In nearly all instances, there was a moderate to marked decrease in blood pressure. The absolute decrease in blood pressure was many times normal, and the percentile decrease in blood pressure averaged three to four times that which characterized the normal individuals. In some instances, the diastolic pressure of the hypertensive subjects decreased to well below the normal level. There was usually an increase in pulse rate roughly proportional to the decrease in blood pressure.

Two observations seemed to indicate that the hyper-response to acetyl-beta-methylcholine might be related to the physiologic basis for the hypertension. There were 6 patients whose blood pressures, under resting conditions, had decreased to normal at the time our observations were made. These, none the less, experienced a definitely greater percentile decrease in blood pressure than did the non-hypertensive individuals. It therefore seems clear that the greater percentile decrease in blood pressure is independent of a high primary level of blood pressure and is probably related to the hypertensive disease. Another patient, whose diagnosis seemed to belong to the ordinary Group 2 of essential hypertension (Table 2, Case 24), on two separate occasions experienced no significant changes in blood pressure in response to the drug. We wonder if the hypertension of that individual rests upon a different physiologic basis than the hypertension of the other patients so tested.

TABLE 3.—HYPERTENSIVE PATIENTS: EFFECT OF MECHOLYL, 2.5 MG., SUBCUTANEOUSLY ON COLD PRESSOR RESPONSE.

Case.	Sex.	Age.	Resting B. P.	Highest B.P. during cold test.	Lowest B. P. after mecharyl.	Highest B.P. during cold test after mecharyl.
27	M	45	124/76	148/128	104/70	126/102
28	M	28	160/80	202/130	130/60	182/80
29	F	60	182/90	208/100	130/68	152/74
31	F	41	134/90	150/110	114/66	114/70
32	M	28	196/130	204/140	164/114	180/124
34	F	34	184/130	226/180	146/92	184/124

Since the sudden and often abnormal elevation of blood pressure, which is usually experienced by hypertensive subjects in response to placing the hand in ice-water, is thought to be the result of a generalized reflex vasoconstriction, we have tested the effect of acetyl-beta-methylcholine upon this response. After having patients perform the cold water test in the usual manner and allowing sufficient time for the blood pressure to return to the control level, we

administered 2.5 mg. of the drug. As soon as a considerable decrease in blood pressure had occurred, we repeated the cold test and compared the result of the second test to that of the first. The results of our observations are given in Table 3. In every instance the reflex vasoconstrictor response of hypertensive patients to cold was markedly reduced after administering acetyl-beta-methylcholine.

The decrease in blood pressure and the abolition of the vasoconstrictor response to the cold test that occurs during general anesthesia are thought to be caused largely by a maximal diminution of the nervous control over the blood-vessels, including a nearly complete diminution of the nervous vasoconstrictor influence. We have compared the decrease in the blood pressure of hypertensive patients during anesthesia induced by the intravenous injection of pentothal sodium to that occurring after the subcutaneous administration of 2.5 mg. of acetyl-beta-methylcholine. The results of our observations are given in Table 4. In every instance, the subcutaneous administration of acetyl-beta-methylcholine in a dose that scarcely affected the level of blood pressure of a normal subject, caused a decrease in the blood pressure of hypertensive patients to a lower reading than that resulting from deep anesthesia, induced by the administration of pentothal sodium.

TABLE 4.—HYPERTENSIVE PATIENTS: A COMPARISON OF THE FALL IN BLOOD PRESSURE RESULTING FROM INTRAVENOUS ANESTHESIA (PENTOTHAL SODIUM) TO THAT RESULTING FROM THE SUBCUTANEOUS ADMINISTRATION OF MECHOLYL, 2.5 MG.

Case.	Resting B. P.	Lowest B. P. during anesthesia.	Resting B. P.	Lowest B. P. after mecholyt.	Percentile decrease* in diastolic B.P.	
					Anes- thesia.	Mech- olyt.
3	230/140	134/98	180/108	132/78	30.0	27.8
7	214/126	160/114	164/106	120/76	9.5	28.3
4	206/140	160/124	200/140	166/114	11.4	18.6
11	176/126	154/110	158/108	130/84	12.7	22.2
16	224/120	150/80	170/100	144/74	33.3	26.0
18	170/120	138/106	158/120	120/90	11.7	25.0
19	188/124	140/110	156/112	138/80	11.3	28.6
30	154/98	140/98	144/104	124/64	0	38.5
32	160/110	144/110	186/126	166/100	0	20.6
34	208/142	160/124	194/132	146/92	12.7	30.3

* Pressure compared with resting pressure.

We have made a similar comparative study of the blood pressure responses to the intravenous administration of acetyl-beta-methylcholine of both normal dogs and dogs having experimentally induced renal hypertension. The introduction of the Goldblatt method of producing a persistent hypertension in animals has furnished opportunities for the study of experimental hypertension. It has become exceedingly important to know whether this type of hypertension as it affects animals is similar to the common types of hypertension

affecting man. For this reason, it is desirable to undertake any method of comparing the two states.

These observations were made under the direction of Dr. H. E. Essex and Dr. J. F. Herrick at the Institute of Experimental Medicine of The Mayo Foundation. The blood pressures were recorded by the intra-arterial method of Hamilton⁹ and associates. The acetyl-beta-methylcholine was administered intravenously in doses small enough to produce less than a 20% decrease in blood pressure, as well as in larger doses to produce up to a 50% decrease, so as to provide a better comparison and to show that the vessels of hypertensive dogs were dilatable. Results of these studies are given in Table 5. It appears from our observations that the percentile decrease in blood pressure in response to the administration of acetyl-beta-methylcholine is no greater in dogs having experimentally induced renal hypertension than it is in normal dogs. In this respect, this type of experimentally induced hypertension seemingly differs from the common types of hypertension which affect man.

TABLE 5.—NORMAL AND HYPERTENSIVE DOGS: RESPONSE TO INTRAVENOUS ADMINISTRATION OF MECHOLYL.

No. of dog.	Weight in kg.	Dose in mg.	Control B. P.	B. P. after mecholyl.	Percentile decrease.†	
					Sys-tolic.	Dias-tolic.
T 437*	12.25	0.0014	261/146	228/120	12.6	17.8
		0.0028	278/151	202/106	27.3	29.8
		0.075	263/142	131/65	50.2	54.2
T 438*	9.5	0.0012	243/119	199/98	18.1	17.6
		0.0024	246/120	179/84	27.2	30.0
		0.060	260/115	124/56	52.3	51.3
T 542‡	18.0	0.002	210/111	173/90	17.6	18.9
		0.004	224/117	148/80	33.9	31.6
		0.1	214/118	99/61	53.7	48.3
T 633‡	21.5	0.002	224/110	144/80	35.7	27.3
		0.004	223/117	134/68	39.9	41.9
		0.1	217/116	102/51	53.0	56.0

* Hypertensive.

† Pressure after mecholyl compared to control pressure.

‡ Normal.

Summary. In summary, we believe that our observations demonstrate almost certainly that the peripheral blood-vessels of most hypertensive patients react by a greater proportional dilatation in response to the administration of acetyl-beta-methylcholine than do the blood-vessels of normal individuals. It is difficult to understand how peripheral blood-vessels which display a hyperdilatation in response to the administration of choline derivatives can be maintained in a state of increased tone in the case of hypertensive individuals, unless we assume that the concentration of acetylcholine at the nerve-endings of the cholinergic vasodilator nerves of these patients is subnormal. We present these observations in support of the hypothesis that a deficient acetylcholine-vasodilator mechanism may be a factor in the production of the arterial

hypertension of man. It would seem that this approach to the study of mechanisms for the production of hypertension deserves further investigation.

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CHRONIC HYPERTROPHIC SPINAL PACHYMEINGITIS.

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ALTHOUGH not an extremely rare condition, chronic hypertrophic spinal pachymeningitis is frequently overlooked in the differential diagnosis of certain spinal cord syndromes. Its diagnosis, though difficult, is important, since the condition is often surgically or medically remediable. Since 1926, when Moniz¹⁵ reviewed the subject from the studies of Charcot,⁶ up to 1925, little attention has been given the subject in English or American literature, and most of the foreign articles have consisted of single case reports.

We have collected 15 cases of hypertrophic spinal pachymeningitis (12 with autopsies), and feel that this number affords an opportunity to summarize some of the outstanding clinical and pathologic features of the condition. Moreover, it would perhaps be pertinent here to review briefly some of the current opinions regarding hypertrophic spinal pachymeningitis.

Etiology. Syphilis is generally conceded to outrank other etiological agents,^{2,3,24} tuberculosis being next in frequency. Besides these causes, however, the meningitides,^{1,2} neighboring or remotely situated, pyogenic and other types of infections are thought to affect the meninges in a similar manner.^{4,9,10,13,17,18,26,27} Trauma has been ascribed an etiologic rôle by Pommé *et al.*¹⁹ and Richard *et al.*²¹ and was apparently the precipitating cause in 1 of our cases. Pachymeningitis has often been associated with true syringomyelia (occurring in 1 case of our series) but whether a mere associated congenital phenomenon or a cause of the syringomyelia itself by vascular interference is a nice question which is discussed by Moniz.¹⁵ Lorey and Schaltenbrand¹⁴ have raised the question of Roentgen ray irradiation's causing pachymeningitis. Finally, the etiology of certain cases of pachymeningitis has to be ascribed to a "cryptogenic" category.^{6,7,19}

Pathology. As its name implies, hypertrophic spinal pachymeningitis is a chronic inflammatory reaction, consisting essentially of a fibrous hyperplasia of the dura often with perivascular and interstitial lymphocytic infiltration. The inner surface of the dura undergoes hyperplasia and sometimes attains 5 to 10 times its normal thickness. The underlying piaarachnoid is usually involved in this process; and the cord, leptomeninges and dura become mutually adherent. Calcium deposition and hyalinization are sometimes observed.¹⁵ The spinal roots are often enmeshed in dense adhesions and may show degenerative changes. The cord itself shows varying degrees of myelomalacia, with demyelination especially of the posterior columns, dorsal and ventral spinocerebellar tracts, while different stages of degeneration are observed in the ganglion cells. Passive congestion and perivascular round-cell infiltration are sometimes observed in the intrinsic vessels of the cord.¹⁸ The degenerative changes are apt to be found in segments considerably above and below the apparent clinical "level;"¹⁵ and, although the disease has a particular affinity for the lower cervical region, any portion of the spinal or intracranial meninges may be affected. Cavity formation in the cord is not infrequently observed, and is generally thought to be due to degenerations secondary to embarrassed blood supply.¹⁵

Symptomatology and Diagnosis. From a clinical neurologic standpoint, the symptomatology has no pathognomonic features, and may vary from day to day. This variability made some consider hysteria in 2 of our cases. The usual symptoms consist of root pain and atrophy of the muscles with hypoflexia or areflexia in the distribution of the roots and segments involved and with pyramidal tract signs below and not infrequently above this level. The sensory loss may be of a dissociated type. Ataxia was a prominent symptom in our series. Vesical dysfunction is not infrequent.

Ordinary Roentgen rays of the vertebral column reveal nothing

characteristic except in cases of Pott's disease, vertebral trauma, and in certain cases of syringomyelia where associated congenital bony anomalies may be present. The great majority of authors agree, however, that Roentgen studies after lipiodol injection offer possibly the best means of strengthening the diagnosis preoperatively. In the foreign literature the findings are usually described as partial block at the clinical level, with streaking and breaking up of the lipiodol column;^{8,15} and with retardation of its passage below the level under suspicion, most of the injections having been into the cisterna magna. This procedure is attended with a certain risk of phrenic paralysis. Siebner²³ has reported on a death occurring 12 hours afterwards.

Spinal manometry and examination of the cerebrospinal fluid are of little help in excluding cord tumor, except that a partial block may be suggestive, and where this is the case in the presence of a positive serology, one is justly suspicious. The total protein content is usually reported as elevated and is regarded as an expression of an inflammatory exudate, local venous stasis with transudation of plasma proteins, stagnation of the fluid below a block or a combination of these factors. Richard, Dechaume and Croizat²¹ report a marked decrease in the protein after a decompression in their case. In the more active inflammatory types of the disorder the cell count as well as the protein is apt to be elevated. The colloidal gold curve is usually abnormal but, except in luetic cases, presents no specific picture.

With syphilis and tuberculosis excluded, the chief difficulty is the differentiation from cord tumor. Here Moniz emphasizes the value of lipiodol: 1, Once the lipiodol passes a tumor there is an undelayed "sheer drop" into the sacral cul-de-sac, but in pachymeningitis, consecutive examinations over several days may reveal particles of oil suspended at varying regions below the clinical level; 2, motor symptoms above the level of the lipiodol block argue against tumor; 3, lipiodol produces a transient exacerbation of segmental symptoms in the case of a chronic inflammatory process, while this is much less apt to occur in tumor. Moreover, it is probable that a number of laminectomies have been performed on such cases in the anticipation of finding cord tumor. Several foreign writers have reported their preoperative diagnostic errors in confusing pachymeningitis with neoplasm and we feel a similar humility in stating that the condition was merely "suspected" in only one of our group of 12 autopsied cases.

Treatment. So-called "arachnoiditis," which in certain instances is even a questionable entity, is similar though hardly comparable to hypertrophic spinal pachymeningitis in degree of severity. In the latter condition one is faced with a definitely and progressively thickening dura, and with the prospect sooner or later of a complete transverse myelomalacia. We share the general conviction

FIG. 1

FIG. 2

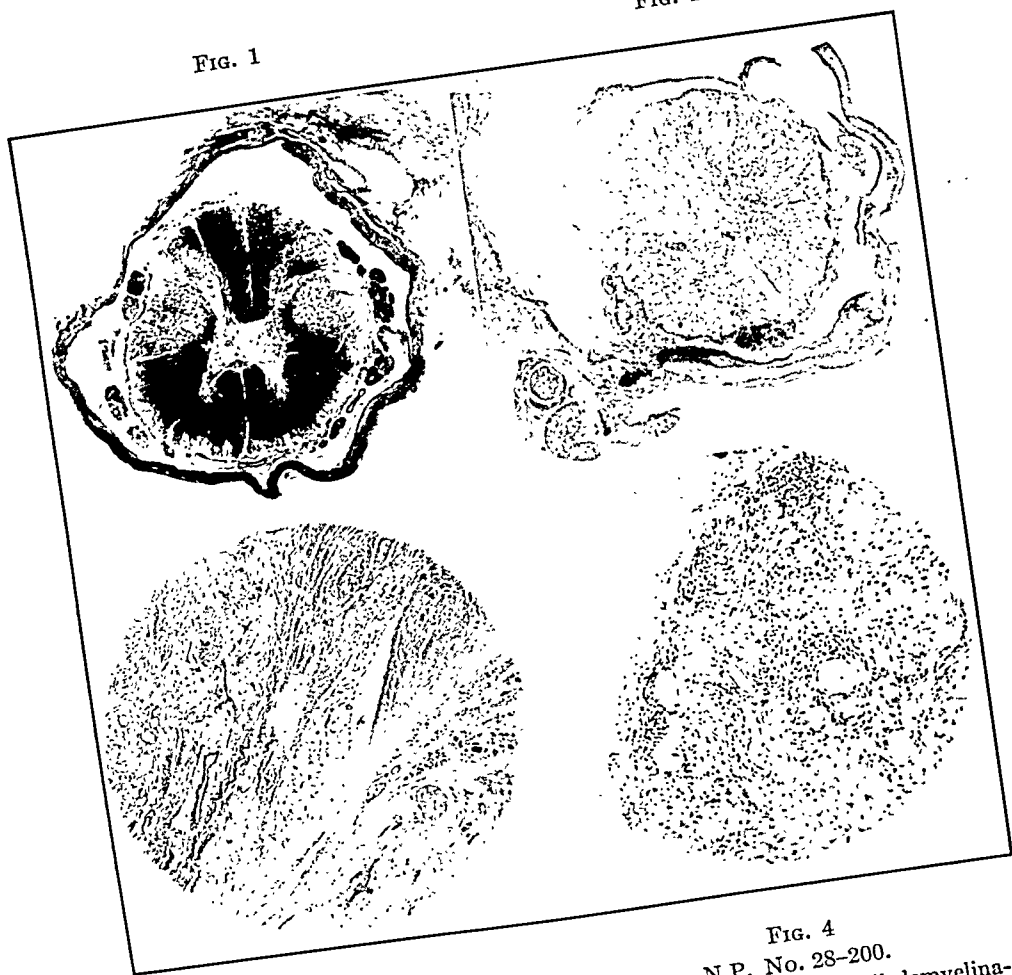


FIG. 3

FIG. 4

HYPERTROPHIC SPINAL PACHYMENINGITIS—N.P. No. 28-200.

FIG. 1.—Dural thickening. Pyramidal, posterior column, and "rim" demyelination. (Weigert—12x.)

FIG. 2.—Intrinsic congestion and degeneration. Implication of roots in adhesions. (Van Gieson—12x.)

FIG. 3.—Dura: Fibrosis and areas of hyalinization. (H. & E.—27x.)

FIG. 4.—Leptomeninges: Interstitial and perivascular lymphocytic infiltration. Fibroblastic reaction. (Nissl—102x.)

that a rational therapy should be one directed toward the arrest or eradication of the compression of the cord or of its blood supply.

In accord with Capani,⁵ we feel that vigorous antiluetic therapy in syphilitic cases merits a clinical trial first. This, however, could hardly be expected to accomplish more than an arrest of the pathologic process with possible return of neural functions where irreversible changes had not yet occurred. It is difficult, however, to conceive of any medicinal therapy which would effect the dissolution of a strangulating ring of thickened dura. The recent literature has contained little reference to the treatment of pachymeningitis (as such) of tuberculous etiology.

Most authors agree that laminectomy and splitting the dura for decompression is the therapeutic procedure of choice in the non-tuberculous and non-luetic cases. Moreover, Puente, Orlando and Dowling²⁰ report improvement from such a procedure in a case of heredolues. Crouzon,⁷ Joisten,¹¹ Veraguth,²⁵ Pommé,¹⁹ Richard *et al.*²¹ and others^{12,17,22} report both subjective and objective improvement in cases after operative intervention. Knust and Salus, in surveying the literature in 1931, indicate that 10 of 16 cases operated have been either improved or cured.

Method of Study. Correlations of the clinical features of 15 cases of chronic hypertrophic spinal meningitis and of the gross and microscopic pathologic findings on 12 of these cases were tabulated. The diagnosis in 3 instances was clinical; in the remaining 12 cases, however, pathologic, being based on a relatively localized pronounced thickening of the spinal dura to a degree apparently sufficient to account for the clinical signs pointing to this level. Dural thickenings associated with acute inflammation such as pyogenic osteomyelitis were omitted from this study. "Brain symptoms" refers to those cases showing gross mental aberrations, cranial nerve dysfunctions, or both.

TABLE 1.—ETIOLOGIC FEATURES IN CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS (15 CASES).

<i>Age range</i> (21 to 65):		
20-30	.	4
30-40	.	4
40-50	.	1
50-60	.	4
60-70	.	2
<i>Sex:</i> Female	.	5
Male	.	10
<i>Etiology:</i> Lues	.	8
BWR (alone)	.	2
CSF	.	6
T.B.	.	2
Undetermined	.	5
Trauma (?)	.	1
Associated with syringomyelia	.	2

Results. Etiologic factors are presented in Table 1. Table 2 assays a correlation of certain clinical features with the nature and location of the spinal lesions, indicating that clinically the prominence of pain, sensory disturbances, ataxia, pyramidal and lower

motor neuron symptoms, and vesical dysfunction all had adequate pathologic bases. Table 3 correlates the clinical and pathologic diagnosis on the 12 autopsied cases.

TABLE 2.—NUMERICAL CORRELATION OF CLINICAL AND PATHOLOGIC FEATURES OF CHRONIC HYPERTROPHIC SPINAL PACHYMEINGITIS.

<i>Clinical Features (15 Cases).</i>		<i>Pathologic Features (12 Cases).</i>	
Symptoms.	No. of cases.	Findings.	No. of cases.
Pain	8	Dura thickened	12
Sensory disturbance	11	Piaârach. thickened	10
Sensory(?) disturbance	2	Degen. post. horn cells	11
Ataxia	11	Demyelin. sp. thal. tr.	7
Upper extremities	2	Demyelin. post. col.	12
Lower extremities	8	Dors. sp. cerebell.	10
Both upper and lower extremities	1	Ventral sp. cerebell.	7
Pyramidal	13	Demyel. pyr. tract	8
Vesical dysfunction	9	Demyel. pyr. tract(?)	8
Retention	4		
Incontinence(?)	4		
Unspecified	1		
Lower m. neuron	9	Anterior horn cell degen.	12
Atrophy	5		
Fibrillation	3		
Flaccidity	2		
Only hyporeflexia	2		
Brain symptoms	10	Miscellaneous:	
		Cavitation of cord	4
		Hemorrhage	0
		Thrombosis	1
		Perivascular infiltration of meninges	11

TABLE 3.—CORRELATION OF CLINICAL DIAGNOSES AND PATHOLOGIC FINDINGS IN 12 AUTOPSIED CASES SHOWING CHRONIC HYPERTROPHIC SPINAL PACHYMEINGITIS.

Case No.	Clinical diagnosis.	Pathologic diagnosis.
1. 705*	Incomplete myelitis	Pachymeningitis and syringomyelia
2. 727*	Syringomyelia (non-traumatic)	Pachymeningitis and syringomyelia
3. 23-155	Cerebrospinal syphilis	Generalized hypertr. pachy. and C.S. syphilis
4. 29-310	Syph. meningo-myelitis	Pachymeningitis—mid-thoracic
5. 24-81	Tabo-paresis	Cerebrospinal lues—pachym. cervicalis
6. 28-19†	Myelitis or cord tumor	Hypertrophic pachymeningitis
7. 28-200†	Arachnitis or cord tumor	Pachymeningitis and myelomalacia
8. 30-50	Transverse myelitis	Thickening of thoracic dura with myelomalacia
9. 30-301	Transverse myelitis	Pachymeningitis — lumbar cord — myelomalacia
10. 33-172	Tabo-paresis	Pachymeningitis cord. Pial fibrosis of brain
11. 35-251	C.N.S. lues	Pachymeningitis dorso-lumbar cord. Stenosis of 4th ventricle
12. 36-155	Amytrophic lat. scl.	Meningo-vasc. syph. hypertr. pachy. dorsalis

* Univ. of Penna. cases; remaining cases from Phila. Gen. Hosp.

† Underwent laminectomy (oper. diag.).

Discussion. No symptom or syndrome may be regarded as pathognomonic. In fact, from our case studies, luetic hypertrophic

pachymeningitis, although showing an affinity for the cervical and dorsal regions, cannot often be regarded as an exclusively localized process, but rather as a regional manifestation of a usually more generalized meningovascular syphilis. In 10 of our 15 cases definite brain symptoms were clinically manifest.

In 2 of our cases the clinical picture so closely simulated cord tumor that laminectomies were performed. One of these cases showed partial block and negative serology and the other showed no block, negative spinal fluid Wassermann, but signs of fairly definite level (the blood Wassermann in this case was positive, however). Correlating the clinical and pathologic diagnoses in the 12 cases autopsied, we were impressed by the fact that in only 1 instance was any clinical mention made of pachymeningitis, the clinical diagnoses being "myelitis," "cerebrospinal syphilis," "taboparesis," and in 1 instance a diagnosis of amyotrophic lateral sclerosis was made. The term "myelitis" in these cases, we feel, not only is a pathologic misnomer, but detracts attention from the nature of the process. It also invites an easy but sometimes unjustifiable therapeutic pessimism. The major pathologic process is in the meninges, and cord changes are largely secondary to embarrassed blood supply or direct compression of the roots or rim of the cord. If medical therapy fails, we feel that surgical decompression should be given more serious consideration in such cases.

Summary. 1. The pathologic incidence of chronic spinal hypertrophic pachymeningitis far outranks its clinical detection, the latter being of some importance as the syndrome may simulate cord tumor. Moreover, pachymeningitis itself is not infrequently surgically remediable.

2. A clinical study of 15 cases of chronic hypertrophic spinal pachymeningitis with a pathologic correlation of 12 of these cases is presented.

3. The outstanding clinical features of an "ideal case" appear to be: adult age, male, lues, radicular pain, ill-defined sensory level, ataxia as the most prominent cord symptom, pyramidal and vesical symptoms, intracranial signs, lower motor neuron signs more widespread than at the apparent sensory level, with a partial block on spinal manometry and certain features of lipiodol study as emphasized by Moniz.

4. The characteristic pathologic features are lymphocytic infiltration and fibrous hyperplasia of the dura which may be adherent to the piaarachnoid, compression of the spinal roots and secondary degeneration of the cord, particularly of the posterior columns and the dorsal and ventral spinocerebellar tracts; chronic circulatory insufficiency with resultant myelomalacia of the gray and white matter over several segments above and below the level of greatest involvement.

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A STUDY OF THE QUICK METHOD FOR THE QUANTITATIVE DETERMINATION OF PROTHROMBIN WITH SUGGESTED MODIFICATIONS.*

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RECENT communications by Quick, Stanley-Brown and Bancroft,¹⁴ Warner, Brinkhous and Smith,^{24a} and Dam and Glavind^{5a} have described various methods for the quantitative determination of prothrombin. Although all of these methods employ unphysiological procedures and measure the amount of prothrombin indirectly, the data suggest that such a test has practical clinical importance. Subsequent studies have led these investigators^{2,5b,13a} to conclude that the defect in the coagulation of the blood in certain cases of jaundice is due to a deficiency of prothrombin. Prothrombin estimations have been used to determine which cases of biliary tract disease possess a hemorrhagic diathesis and to study the efficacy of various therapeutic agents in the treatment of this condition. The newer

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methods have also been used to examine the relative amounts of prothrombin in hemorrhagic chick disease of dietary origin, in hemorrhagic disease of the newborn, in toxic sweet clover disease, in hepatic injury due to chloroform intoxication, in subjects with biliary fistula, and in other hemorrhagic diseases.

The present investigations were limited to a critical study of the Quick method for the quantitative determination of prothrombin. Quick and his co-workers^{13a,b,14} and others^{24b} state that the coagulation time of oxalated plasma, when mixed with an excess of thromboplastin and then recalcified, is a measure of the amount of prothrombin present. The importance of using an optimal amount of calcium for recalcification has been emphasized in a preliminary report.²¹ The present observations present more data on the effect of calcium, suggest certain modifications and call attention to errors to be avoided in an effort to provide a simple and more accurate method of determining plasma prothrombin. Prothrombin values on a group of patients with liver and biliary tract disease are presented.

Methods. The present studies were limited to observations on human subjects. The methods followed were essentially the same as those described by Quick.^{13a,c} The prothrombin time was determined on 0.1 cc. portions of oxalated plasma in clean, dry 100 by 13 mm. test tubes in a water bath at 37.5° C. A constant temperature was found to be essential. An excess of thromboplastin was supplied by the addition of 0.1 cc. of a freshly prepared saline suspension of tissue extract from rabbit brain. One-tenth cubic centimeter of an optimal calcium chloride solution was added with a blow pipette, and the time required for coagulation after the addition of calcium was observed with a stopwatch. It was noted that the end-point was always sharp and definite regardless of whether the time was normal or prolonged. Hereafter in this communication any determination of the prothrombin time includes the addition of an excess of thromboplastin in the above manner.

The thromboplastin was prepared from fresh rabbit brain by extraction with acetone U.S.P. as described by Quick.^{13a} This preparation proved to be a satisfactory source of a potent tissue extract. It remained stable in a dry form at 5° C. for approximately 4 weeks. A more uniform preparation of the saline suspension of dehydrated material was obtained if it was incubated at 50° C. for 15 minutes, rather than at 45° C. for 10 minutes as Quick^{13a} advised. Thromboplastin thus prepared failed to cause coagulation when mixed with fibrinogen and calcium.

Experimental. *Effect of Calcium Concentration.* Variable prothrombin times were obtained with normal plasma when the recalcification process was carried out with 0.1 cc. of the 0.025 M calcium chloride solution used by Quick.^{13a,d} Usually it was impossible to obtain a fibrin clot in normal plasma in from 12 to 13 seconds unless the concentration of calcium was altered.

A stock solution of 0.1 M calcium chloride was prepared by dissolving 1.11 gm. of anhydrous chemically pure calcium chloride in 100 cc. of distilled water. Eleven solutions of calcium chloride, varying in concentration from 0.1 M to 0.000625 M, were prepared by diluting this stock solution. The effect of each of these solutions as a

recalcifying agent in determining the Quick prothrombin time was studied on the plasma obtained from 85 normal subjects.* The results obtained in each subject were similar. The observations on 1 typical case are shown in Table 1. The data obtained on a case of obstructive jaundice with a hemorrhagic diathesis are presented in this table for comparison. The findings clearly show that an excess of calcium as well as an insufficient amount of calcium prolonged the coagulation time. The optimal amount of calcium which was required to obtain a minimal coagulation time varied from individual to individual although usually recalcification with 0.1 cc. of a 0.01 M, 0.005 M or 0.0025 M calcium chloride solution was optimum. With optimal recalcification the normal prothrombin time was found to be 10 seconds. Not a single individual in the group of 85 normal persons studied showed a prothrombin time longer than 10 seconds. A coagulation time slightly shorter than 10 seconds was occasionally observed. Under these circumstances it appears reasonable to conclude that a 10-second prothrombin time may be considered to indicate the presence of 100% prothrombin.

TABLE 1.—EFFECT OF CALCIUM CONCENTRATION ON PROTHROMBIN TIME OF PLASMA FROM A NORMAL AND ABNORMAL SUBJECT.

Molar concentration of calcium chloride.	Coagulation time in seconds.	
	Normal.	Jaundice.
0.1	46	340
.05	22	73
.033	15½	49½
.025	14	40
.02	13	38
.015	12	32
.01	11	32
.005	10	29
.0025	10½	29
.00125	18	50
.000625	38½	124

The effect of calcium concentration was more critically studied on plasma obtained from 6 normal subjects in an effort to compare the optimal amount required for the determination of the prothrombin time with the total calcium of the blood serum. The amount of calcium present in the plasma after oxalation varied from 0.5 to 2.0 mg. per 100 cc. Most of the calcium oxalate was thrown down with the blood cells during centrifugation. The calcium chloride solution for this particular experiment was prepared by dissolving 2.5 gm. of reagent pure precipitated calcium carbonate in a slight excess of N hydrochloric acid. The slight excess acid was neutralized to pH 7.4 by the addition of 0.1 N sodium hydroxide and made up to 1000 cc. with distilled water. One cc. of this solution contained

* In all the prothrombin values presented in this communication this same technique for recalcification was followed.

1 mg. of calcium in the form of calcium chloride. A series of 21 calcium chloride solutions was prepared from this solution in such concentrations that when 0.1 cc. was mixed with 0.1 cc. of thromboplastin and 0.1 cc. of plasma, the calcium concentration varied from 3 to 17 mg. per 100 cc. When the calcium concentration was between 8 and 13 mg. per 100 cc., a normal 10 second prothrombin time was obtained on each of the 6 plasmas tested. The prothrombin times obtained when the calcium values were less than 8 and more than 13 mg. per 100 cc. were prolonged. Therefore, although the recalcification of plasma is an artificial process, the optimal amount of calcium required for coagulation *in vitro* was very similar to normal blood serum values for calcium.

Effect of Oxalate Concentration. The effect of oxalate concentration on the prothrombin time was studied on the plasma obtained from 6 normal individuals. Four and a half cubic centimeter samples of blood obtained by venipuncture were immediately mixed with 0.3, 0.4, 0.5, and 0.6 cc. respectively of a solution of 0.1 M sodium oxalate and centrifuged. The prothrombin time was determined in the usual manner on each of these plasmas. The results showed that the amount of calcium required to form a fibrin clot in 10 seconds varied slightly in proportion to the amount of oxalate present. However, since the optimal amount of calcium was determined in each instance, slight variations in the oxalate concentrations would not affect the prothrombin time. In all subsequent studies a 4.5 cc. sample of venous blood was oxalated with 0.5 cc. of 0.1 M sodium oxalate solution as described.^{13a}

Simultaneous determinations of prothrombin were made on normal plasma which had been oxalated with equal amounts of 0.1 M sodium oxalate in the wet and in the dry forms. There was no essential difference in the results.

TABLE 2.—EFFECT OF LIPEMIA ON PROTHROMBIN TIME OF NORMAL PLASMA.

Molar concentration of calcium chloride.	Coagulation time in seconds.	
	Clear plasma.	Grossly lipemic plasma.
0.1	38	32
.05	17	15
.033	13	12½
.025	12½	10
.02	12	10½
.015	11	9
.01	11	9
.005	10	8½
.0025	10	8½
.00125	15½	9½
.000625	29	20

Effect of Lipemia. During the course of these observations it was noted that normal plasma possessing a gross lipemia frequently had a prothrombin time of less than 10 seconds. Prothrombin determina-

tions were made upon 3 individuals immediately after taking a low fat diet for a period of 24 hours. Each subject was then given a meal containing 120 gm. of fat and the prothrombin reading was repeated after 2 hours. The plasma obtained 2 hours after the high fat meal showed a gross lipemia. The results in one typical experiment are shown in Table 2. These data suggest that a markedly lipemic plasma has a shorter prothrombin time than clear plasma. The explanation of this phenomenon is not clear.

Relation Between the Prothrombin Time and the Concentration of Prothrombin. Since these studies indicated that with optimal recalcification the normal prothrombin time was 10 seconds rather than 12 to 13 seconds, it was necessary to reconstruct the graph permitting

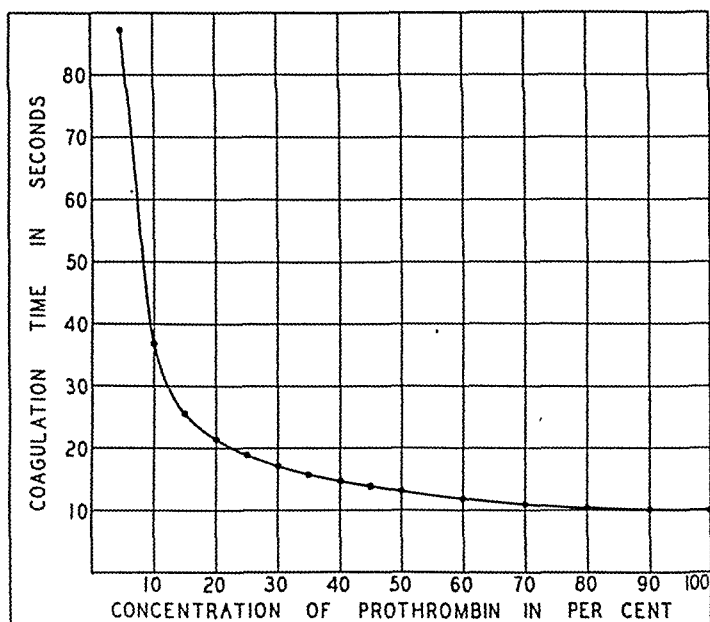


FIG. 1.—Relation of the prothrombin time, determined by the modified Quick method, to the concentration of prothrombin in human plasma.

the conversion of the prothrombin time to the percentage concentration of prothrombin. The data for the graph devised by Quick^{13a} were obtained by determining the prothrombin time of various dilutions of normal plasma, with saline, or with other plasma rendered free of prothrombin by treatment with aluminum hydroxide.^{13b,c,14} While repeating these studies with saline dilutions of plasma it was always noted that it was difficult to judge the time of clot formation in the dilutions containing 30% or less plasma because of the slow and scanty fibrin formation. Under these conditions a reduction in prothrombin was accompanied by a similar reduction in fibrinogen. This alteration of the amount of fibrinogen introduced an error into the determination of prothrombin since it did not

parallel the usual *in vivo* condition. For example, it is agreed that a significant alteration of fibrinogen does not exist in cases of obstructive jaundice with abnormal bleeding, but recent studies strongly indicate that a prothrombin deficiency is usually present.

Fibrinogen was prepared from normal human oxalated plasma as described by Eagle.^{6a} The material prepared in this manner did not coagulate upon the addition of thromboplastin and calcium. Fibrinogen was dissolved in 0.85% sodium chloride solution so that the final concentration was 600 mg. per 100 cc. Various dilutions of a normal plasma were made with the saline solution of fibrinogen and the prothrombin time determined on each. The maintenance of a fairly constant fibrinogen content in the various plasma dilutions resulted in the formation of a normal fibrin clot with a sharp end-point regardless of the prothrombin time. The procedure was repeated with plasma obtained from 5 other normal young adults of both sexes with very similar results. The prothrombin time obtained with each dilution of plasma from each subject was averaged. Assuming that a 10-second coagulation time was normal and was equivalent to a 100% concentration of prothrombin, these composite figures were converted into graph form (Fig. 1). The graph coincided closely with that presented by Quick^{13a} except that, in general, the prothrombin times were shorter.

Prothrombin Values in Individuals With Liver and Biliary Tract Disease. Abnormally low prothrombin levels have been observed in 23 patients in this clinic with various forms of liver or biliary tract disease. The data are presented in Table 3. A control prothrombin time was done on a normal plasma in every instance. Twenty-three patients with jaundice who had normal prothrombin values are not included. Additional data on the bleeding and blood coagulation times are presented in the table for comparison with the prothrombin estimations. The coagulation times of venous blood were determined by a method previously described¹² which gave normal values of from 6 to 12 minutes. Blood platelet counts and the clot retraction were normal in every case.

In this series, 7 patients showed a definite bleeding tendency. Cases 1, 9, 13, and 17 died as the result of hemorrhage. The bleeding tendency in these 7 individuals was associated with a marked decrease in the prothrombin level. The Ivy⁹ bleeding time was prolonged in 5 of 6 of these cases with abnormal bleeding. The bleeding time by the Duke method was normal in every case. A few patients presented very low prothrombin values and yet escaped actual bleeding. The data are insufficient to establish the prothrombin level at which serious bleeding is to be anticipated. The intensity and duration of the jaundice showed no correlation with the decreased prothrombin values.

Discussion. Howell^{8a} first described a method for measuring plasma prothrombin. This method consisted of noting the time

required for coagulation after the recalcification of plasma. Recently 3 more satisfactory methods for the quantitative determination of prothrombin have been described and applied to clinical investigations. The method described by Quick^{13a} improved the Howell technique by adding an excess of tissue extract to insure the complete conversion of prothrombin to thrombin. Dam and Glavind^{5a,b}

TABLE 3.—PROTHROMBIN VALUES IN INDIVIDUALS WITH LIVER OR BILIARY TRACT DISEASE.

Case.	Diagnosis.	Prothrombin, %.	Icterus index.	Coagulation time in minutes.	Bleeding time (Duke) in minutes.	Bleeding time (Ivy) in minutes.	Bleeding tendency.
1	Common duct stone†	35	20	7	3	3	Died postop. of intra-abd. hem.
2	Common duct stone*	72	90	12	1	5	None
3	Common duct stone*	60	25	8	$\frac{1}{2}$	4	None
4	Common duct stone (Ball valve)* .	80	15	..	1	..	None
5	Common duct stone*	65	75	..	1	..	None
6	Adhesions about common bile duct*	30	80	12	1	6 $\frac{1}{2}$	Subconjunctival hem. Gums bled
7	Adhesions about common bile duct*	72	45	8	2	3	None
8	Congenital absence of bile ducts* .	15	50	..	2	..	None
9	Carcinoma of pancreas†	16	200	20	3	13	Died of subd. hemat.
10	Carcinoma of pancreas*	40	45	9	1 $\frac{1}{2}$	6 $\frac{1}{2}$	None
11	Cholelithiasis*	15	60	10	$\frac{1}{2}$	9 $\frac{1}{2}$	Bled excessively from operative wound
12	Cholelithiasis*	65	2	..	1	..	None
13	Cholelithiasis†	15	12	..	2 $\frac{1}{2}$..	Died postop. of intra-abd. hem.
14	Chronic cholecystitis*	35	20	10	1	5	None
15	Liver abscess with biliary fistula* .	28	75	13	1	21	Bled excessively from operative wound
16	Atrophic cirrhosis of liver . . .	25	50	6 $\frac{1}{2}$	2	4	None
17	Cirrhosis of liver†	9	75	12	$\frac{1}{2}$	5	Died postop. of intra-abd. hem.
18	Atrophic cirrhosis of liver . . .	40	7	12	$\frac{1}{2}$	5	None
19	Atrophic cirrhosis of liver . . .	50	20	10	1 $\frac{1}{2}$	2	None
20	Atrophic cirrhosis of liver . . .	47	35	12	1	5	None
21	Atrophic cirrhosis of liver . . .	38	15	10	2	5	None
22	Atrophic cirrhosis of liver . . .	50	18	8	1	3	None
23	Acute catarrhal jaundice	70	25	8	1	7	None

* Denotes operative diagnosis.

† Denotes autopsy diagnosis.

revised the method described by Schönheyder,¹⁸ and estimate prothrombin in terms of the amount of standardized tissue extract which it is necessary to add to a heparinized blood sample in order to cause coagulation in 3 minutes. Smith, Warner, and Brinkhous^{19,24a} have developed an elaborate prothrombin method requiring 2 stages. The first stage is concerned with the conversion of

prothrombin to thrombin in a sample of defibrinated plasma. Fibrinogen is then added to serial dilutions of the thrombin solution and the resulting coagulation times are considered to be an index of the prothrombin content of the parent plasma.

The Quick method for the quantitative determination of plasma prothrombin has the advantage of simplicity. Investigations^{3a,b,c,13a,15} have demonstrated its value in the study of the hemorrhagic diathesis in certain cases of jaundice. The test has been criticized because the final reading includes the time required for the conversion of prothrombin to thrombin as well as the time required for the thrombin formed to react with fibrinogen. However, experiences suggest that if the test is limited to human plasma this variable is not of great importance.

It is well known that an excess of any neutral salt preserves the fluidity of the blood. Horne,⁷ Sabbatani,¹⁷ Rettger,¹⁶ and Stassano and Daumas²⁰ observed the anticoagulant properties of large amounts of calcium. The present studies demonstrate that the presence of an excess of calcium as well as an insufficient amount of calcium prolongs the Quick prothrombin time. It was also observed that an excess of sodium chloride or bile salts in the test tube set-up caused prolongation of the prothrombin time. The optimal amount of calcium necessary to give the minimal coagulation time (prothrombin time) varied from individual to individual. The present observations indicate that if calcium chloride solutions of 0.01, 0.005, and 0.0025 M concentrations are used as recalcifying agents, in the determination of prothrombin by the Quick method, the minimal coagulation time will be obtained. Optimal recalcification gives a normal prothrombin time of 10 seconds. It is especially important that the recalcification be optimal when studying pathologic bloods. Although the recalcification of plasma is an artificial and unphysiologic process these data indicate that the optimal calcium concentration necessary for coagulation of oxalated plasma *in vitro* parallels normal blood serum values for calcium. It is suggested that a control prothrombin time on normal plasma should be done on each occasion to assure proper activity of the thromboplastin and the absence of calcium contamination of the glassware.

The nature, source, and mode of action of prothrombin are widely disputed. Prothrombin is known only by its capacity to form thrombin. Some investigators^{4,8b,10,11} identify the source of prothrombin with the platelets as well as plasma; others,^{1,6b} imply that it resides chiefly in the non-cellular plasma. Certain authors²² deny the existence of a prothrombin factor in the coagulation mechanism. Recent evidence^{19,23} indicates that the liver plays an essential rôle in the manufacture of prothrombin. Absolute proof that the newer methods for estimation of plasma prothrombin actually measure this substance is lacking. However, the present observations confirm those of others^{3a,b,c,13a,15} in that the Quick prothrombin method measures a deficiency which frequently exists in certain

individuals with jaundice. Apparently this deficiency is responsible for the bleeding tendency in these cases.

The investigations on patients with low prothrombin values are being continued. The results, with special reference to various therapeutic efforts, will be reported in a future publication.

Conclusions. 1. The Quick method for the quantitative determination of plasma prothrombin contains variables which significantly influence the results of the test.

2. Calcium is an important variable in the Quick prothrombin method. The optimal amount of calcium necessary for recalcification must be determined in each instance to assure a minimal coagulation time (prothrombin time). Studies on the plasma of 85 normal individuals indicate that with optimal recalcification the normal prothrombin time is 10 seconds.

3. The optimal calcium concentration required for the determination of the Quick prothrombin time is similar to normal blood serum calcium values.

4. Slight variations in the oxalate concentration of the plasma do not influence prothrombin determinations if the optimal amount of calcium required is determined in each case.

5. The presence of a gross lipemia significantly shortens the prothrombin time. It is suggested that in order to avoid this variable determinations should be done only on clear plasma.

6. Observations on 46 individuals, with liver or biliary tract disease, indicate that the modified Quick prothrombin method measures a deficiency which frequently exists in these cases, and which is apparently responsible for the bleeding tendency.

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OBSERVATIONS ON HUMAN BLOOD STORED AT 4 TO 6 DEGREES CENTIGRADE.

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THE blood bank idea has been received with considerable enthusiasm both in this country and abroad, and a number of "banks" are now in operation. Until recently, however, no adequate studies of the effect of preservation on the blood have appeared. These recent studies indicate that the enthusiasm for this innovation in transfusion methods is not entirely justified.

Observations on 10 samples of human blood kept at 4° to 6° C. over a period of 20 days are herein reported. The results appear in Table 1. These are in agreement with those of Kolmer⁵ (in so far as they are parallel) and also with those of Rhoads and Panzer.⁸

Blood was received into 20% sodium citrate to make a final concentration of about 0.4%, although in some instances this was 0.6%. The pH of the citrate after sterilization was 8. Of necessity, the bloods were thoroughly shaken whenever samples were to be removed, a procedure believed to accelerate hemolysis. Hemolysis, however, was not obviously more marked in these specimens than in others remaining undisturbed in the refrigerator for an equal number of days, nor did red cell counts, which were made with each hemoglobin determination, show significant decreases. Fragility tests were done on cells that had been washed in 0.85% saline to remove traces of hemoglobin which had diffused on standing. Prothrombin by two methods was done on the citrated blood, and not on oxalated blood as required in the strict technique. Quick⁷ regards Howell's prothrombin time as a measure of the thromboplastin rather than of prothrombin. Howell's method was used, therefore, with the idea of demonstrating in what manner disintegration of the platelets might affect the thromboplastin content of stored blood.

The most important changes observed in these samples of stored blood were an increase in the fragility of the red cells, disintegration of the granulocytes, and impairment of the properties of coagulation, all progressive. The fall in carbon dioxide combining power of the bloods and in blood sugar, although marked, are probably not important items in a transfusion medium. These changes, with the exception of Quick's prothrombin time, began at once and

were well advanced by the fifth day. The alterations in all the bloods were similar in character and magnitude.

On the basis of these observations it is apparent that stored blood should not be used in the treatment of agranulocytic angina, if the expectation is to restore granulocytes. Whether the disintegration products of these cells could still serve as a stimulant to the manufacture of new granulocytes is, of course, a speculation. The same restriction, obviously, should apply to purpura hæmorrhagica and to hemophilia because of the diminution of platelets and their product, to vitamin K deficiency, and probably to all hemorrhagic diatheses. We have had no opportunity, however, of observing the effect of bank blood in these diseases under controlled conditions.

The significance of red cell fragility changes in stored blood is not so easily decided. If the belief of Yorke and Nauss,⁹ of Baker and Dodds¹ and of DeGowin *et al.*,³ that the harmful effects of hemolytic transfusion reactions result from the blocking of renal tubules by hemoglobin precipitated in acid urine, be accepted, blood should not be used after the first or second day of storage. On the other hand, this fragility is only accompanied by a trivial amount of lysis of erythrocytes during storage, probably attributable to the property of plasma to protect against hemolysis. It is important to note, too, that the oxygen capacity of these cells is not impaired. Moreover, the great majority of patients who receive such blood show no evidence of intravascular hemolysis. It appears that jaundice and hemoglobinuria are somewhat more frequent after infusion of stored blood than after fresh blood. Fox⁴ reports an incidence of 14% for the former, 3% for the latter. Such occurrences are not, however, in most instances, accompanied by other evidences of true hemolytic reactions such as chills, fever and impairment of renal function, as might be expected. The hemoglobin in these cases passes out in the urine without any apparent harm, recalling the experiments of Bayliss.²

In 400 consecutive transfusions with stored blood, jaundice or hemoglobinuria of a harmless character, or both, were observed 7 times. They did not appear to be related closely to the age of these bloods, which averaged 10 days, for in 12 other transfusions with an average blood age of 16 days no evidence of hemolysis was observed. In addition, there were 3 classical hemolytic reactions, one of which was due to forwarding the wrong bottle of blood to the ward. Excluding this, our incidence of 2 true hemolytic reactions in 400 transfusions is not significantly greater than that for fresh blood as reported in medical literature. Other reactions occurred, characterized by chills and fever, urticaria, and so on, making an incidence of 10% in all, but these were not accompanied by evidence of hemolysis. A lower reaction rate for refrigerated than for fresh blood is reported from the Mayo Clinic.⁶

It is our opinion, by no means original, that true hemolytic trans-

fusion reactions represent something much more profound than simple intravascular hemolysis. Certainly hemolysis incidental to an acquired fragility of red cells should be distinguished from that of an antigen-antibody type of reaction. If this distinction be justified, then the incompatibilities causing true reactions are, in all probability, the same whether the blood be fresh, or stored; and consequently the danger of reaction with the two types of blood should be equal.

TABLE 1.—OBSERVATIONS ON 10 HUMAN BLOODS COLLECTED IN CITRATE AND STORED AT 4° TO 6° C.

Days	0	1	2	3	4	5	10	15	20
Hemoglobin	13.8	13.7	14.0	13.6	13.4
Oxygen capacity . .	18.8	19.3	18.1	19.4	18.5	18.5	18.5	18.6	18.0
Rbc. fragility . . .	0.44	0.48	0.49	0.60	0.60	0.68	0.75	0.83	0.85
(% NaCl)									
Granulocytes . . .	49	35	33	12	16	9	2	0.3	0.2
(hundreds)									
Prothrombin (Quick)	22	22	28	33	38
Prothrombin (Howell)	168	388	586	640	721
Platelets (thousands)	216	92	44	48	58	60	48	33	33
Isoagglutinin titer	57	57	57	44	27
Plasma CO ₂	43	34	34	26	20	18	12	10	10
Glucose	97	72	55	43	43	33	13	10	?

Isoagglutinins were measured on 9 bloods, plasma CO₂ and glucose on 6. Figures are the average of observations for each day.

It would seem, from the results of this and other studies, that refrigerated blood should be used within a few days of collection, and that the arbitrary limit of 14 days allowed by some is much too long. Since a rapid turnover and prompt use is possible only in institutions performing large numbers of transfusions, 100 or more per month, a blood bank is apparently ill-advised for small hospitals.

Comparison of the therapeutic effects of stored and fresh blood in exact terms is not possible, but a canvass of the clinical staff of this hospital shows general satisfaction with the blood bank.

Summary. Important alterations in human blood stored in a refrigerator (a "blood bank") are recorded.

Such blood is clearly of less therapeutic value in some respects than fresh blood; but it is apparently of equal value in other respects. Its use is not accompanied by greater danger to the recipient than is that of fresh blood.

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THE COLLECTION AND PRESERVATION OF PLACENTAL BLOOD FOR TRANSFUSION PURPOSES.*

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UNTIL the past few years, it always has been thought necessary to collect fresh blood at the time a transfusion was to be given. Recently this technique has changed considerably, and at present in many of the larger medical centers preserved blood has been used extensively. The first reports came from Russia,^{1,11,14,17} where they definitely proved that this blood was usable and of value. There was a demand, however, for a source of supply which would be available in any general hospital. With this in mind they turned to the obstetric department and its potential reservoir of placental blood.^{2,15}

Independently, on this continent, Goodall⁹ and his associates at Montreal started the collection of placental blood while working on an experimental procedure aimed to test the result of the reduction of intraplacental tension on the third stage of labor. They have collected and preserved blood for 2 years and at last reports⁸ they were satisfied with the use of the placental blood for transfusions. It was effective and they had had no untoward reactions. Recently Grodberg and Carey¹⁰ have reported the use of this type of preserved blood at the Boston City Hospital.

We first studied the Montreal technique⁹ and have directed our investigation along the following lines: 1. Development of the technique of collection and preservation; 2, the effect on the mother; 3, assurance of its safety for use; 4, proof of its value.

Collection and Preservation. We have set forth the following conditions which determine the cases suitable for collection of blood: *a*, The mother must be free from transmissible disease; *b*, the membranes must not be ruptured over 48 hours; *c*, there must not be obvious infection; *d*, the baby must be at or near term; *e*, the baby may not have asphyxia pallida; *f*, the presentation may not be breech or transverse.

* Read before the Syracuse Academy of Medicine, December 20, 1938.

Method. All mothers have antepartum Wassermann and flocculation tests of their blood. As an added precaution, blood is taken from the cord after delivery of the placenta for serologic examination.

The equipment we use is as follows: A 6 by 12 in. white enamel tray; a 500 cc. Erlenmeyer flask or Pyrex bottle; a Davol Sani-tab rubber cap; two 65 mm. test tubes; one 75 mm. Pyrex funnel with a special 80 mm. stem; one wood block 4 by 4 by 4 inches in which there are two holes to fit the small test tubes; one towel with a 3 by 3 inch hole, and one medicine glass. This is prepared as follows for collection of blood: The 500 cc. Erlenmeyer flask or Pyrex bottle will be stoppered by the rubber cap which provides an air tight seal and keeps the top of the flask sterile. This flask is placed on the tray lying on its side. In the two holes of the block are the small 65 mm. tubes, one empty and one containing 2 to 3 cc. of preserving fluid. The empty tube is for the collection of serum, and the tube containing the fluid is for a cell-suspension. Wrapped in a towel beside the flask and block is the Pyrex funnel. The towel with the hole in its center and the medicine glass complete the contents of the tray. This set is wrapped and autoclaved for 20 minutes at 15 pounds' pressure. When ready to be used the tray is simply unwrapped and placed on a table beside the sterile delivery table. The scrub nurse removes the contents of this tray to the delivery table, thus maintaining sterility.

The preserving fluid is made up so that each 1000 cc. contains 20 gm. of dextrose, 5 gm. sodium citrate (0.5%) and 4.6 gm. of sodium chloride. C.P. chemicals are used, and the final solution is isotonic. It is made as two solutions—one containing the dextrose, the other the salt and citrate, each in 500 cc. volume. These are then apportioned 50 cc. to a flask and sterilized; then one of each type poured into the collecting flask just before collection of the blood. This method entirely avoids caramelization of the sugar. However, the combined solution is used in the small test tube when the set is made up. Slight caramelization occurs but is not detrimental in preserving the cells for grouping and cross matching.

As soon as the baby is born the cord is clamped and cut. The baby is first attended, and, when its condition is satisfactory, it is placed in the crib. The blood is then collected. The end of the delivery table is partly lowered or in the case of the double table the two portions are separated. The physician who is to collect the blood strips back the last 2 inches of the cord, and, with his hand, holds it at the upper limit of the stripping. The stripped portion of the cord is cleansed with 70% alcohol and the end of the cord is cut off. The towel with the hole in its center is thrown over the operator's hand in such a fashion that the freshly cut tip of the cord and the hand extend through the hole. The towel is now in position to prevent any splashing from the vulva or the rectum from entering the funnel and flask. The assisting nurse has in the meantime placed the funnel into the mouth of the flask and at the proper time holds it beneath the tip of the cord. The blood is allowed to flow freely into the funnel. The operator is careful not to squeeze the cord during this early period of collection, because once the cord is compressed, the blood may stop flowing as coagulation occurs rapidly at the point of injury. During the entire collection the assistant gently agitates the flask with a rotary motion in order to prevent clotting of the blood before it is thoroughly mixed with the preserving fluid. When the flow of blood becomes slow, pressure is applied to the fundus of the uterus through the abdomen to force out the remaining blood. When this is accomplished, the cord is gently stripped until there is no more blood in the vessels. The last bit of blood is collected in the two 65 mm. tubes, 3 drops going into the tube containing the preserving fluid and approximately 1 cc. being collected in the other tube. A third tube is used to collect blood for the cord Wassermann test. The two small tubes are then placed in the

medicine glass. The funnel is removed, and the flask is sealed with the rubber cap. This keeps the top clean during subsequent handling. Once again the blood is thoroughly agitated with a rotary motion to insure complete mixing. The flask and each of the little tubes are labeled with the patient's name, date, and Wassermann reaction, and all are taken to the icebox. The flask is not opened again until the blood is used for a transfusion.

At a convenient time, preferably once every 24 or 48 hours, the new collections of blood are catalogued. The name and date on the flask and the two small test tubes are checked and recorded. The medicine glass containing the small test tubes is taken out of the icebox. The one containing clotted blood is centrifuged and the supernatant serum collected in capillary tubes which are sealed for storage. From the cell suspension in the second tube, the blood group is determined by means of known, potent group A and B sera. The sealed tubes of serum are now placed in the test tube containing the cells, this is labeled to correspond with the large flask, and then is stored according to group in a test tube rack in the icebox. A tag bearing the name, date, serology report and blood group is put on the flask of blood which is placed on the shelf used for blood of that group. A complete record is kept in a loose-leaf book, each blood being listed by its group classification, so that we can rapidly determine the number of flasks on hand in each group, their volumes, ages, and so on. Every flask of blood is kept in storage for 10 days, and then, if its appearance is normal, it is ready for use. By normal appearance is meant: first, that the rubber cap shows the presence of a slight vacuum, and second, that the supernatant plasma and preserving fluid is clear yellow with, at most, a just visible tinge of hemolysis immediately above the layer of settled red cells (the appearance may be slightly cloudy due to incomplete settling of the buffy layer present in citrated blood). If either or both are not present, the collection is discarded as possibly contaminated.

The icebox, which we have used for storage, is equipped with a constant temperature control which maintains 34 to 35° F. This was thought advisable for experimental work. Time has proved that a refrigerator equipped with a condensing unit of greater than standard capacity and a fan to circulate the air in the box will maintain a sufficiently constant temperature for preservation of this blood. It is suggested, where the refrigerator is to be sufficiently large, that the cooling unit be of the air-conditioned type. We say this because the one difficulty with the icebox described above is the problem of defrosting. If the standard refrigerator is used, the defrosting has to be carried on as rapidly as possible in order that the blood does not lose its chill.

Cross-matching and Transfusion. In using the blood for a transfusion, the blood group of the recipient is first determined, and then complete cross-matching is carried out with each of the desired number of flasks containing blood of the same group. This is done with the small tubes of cells and serum, and this method permits of several such tests for compatibility without touching the flask of preserved blood. One-half hour is the minimum time that the cross-matchings must stand before compatibility is passed on, but we prefer to wait 45 to 60 minutes because the reaction time of fetal blood is felt by some men to be slower than that of adult blood. We have not found this to be true so far. In grouping the recipient however, the reaction is usually apparent within 10 minutes and cross-matching can be started almost at once in urgent cases. When this is done, a final reading of the patient's group is always made again at the end of the half hour. In cross-matching and grouping we use the vaseline sealed hanging drop preparation in which drying of the suspension of cells and serum as well as contact with foreign substances or other trauma is eliminated.

The flasks of blood found to be compatible are now removed from the icebox, rotated gently to obtain an even suspension, and then are ready for use. It is not necessary to warm the blood before using it, for it will be nearly at room temperature when it enters the patient's vein. In fact, heating preserved blood may be a factor in producing reactions. Knowing a patient's group, we can at once pick out the needed number of flasks of the same group, and can be almost certain they will prove to be compatible on cross-matching. When the flask is used, the recipient's name and the date of use complete the record. In cases where time is not a factor, we have adopted the routine of giving the recipients enough sodium bicarbonate by mouth or sixth molar sodium *r. lactate* by vein to make the urine reaction alkaline prior to transfusing them, inasmuch as this has been shown to very probably eliminate the danger of anuria by a plugging of the kidney tubules with precipitated free hemoglobin if a reaction producing hemolysis should occur.^{6,13} In emergency cases we make every effort to carry this out.

When the blood is nearly ready an intravenous infusion of isotonic saline is started on the patient, using an open burette of the familiar arsphenamine type as the container. The prepared blood is poured into the burette through a funnel, the top of which is covered by 6 thicknesses of washed sterile gauze, and allowed to run in by gravity. The funnel has been prepared previously and autoclaved with the transfusion set, and, just before using, it is washed by pouring sterile saline through it in order to remove any remaining bits of loose gauze. It is more or less characteristic of preserved blood to have a few small soft clots present in the flask. This may be due to the action of small amounts of Wharton's jelly. These are strained out by the gauze. The second flask of blood is poured into the burette when the first has almost completely run in, and the two may be separated by a small amount of saline solution, although this has not been found to be necessary. It is our practice to wash the last of the blood into the patient's vein with addition of some saline. The speed at which the blood is allowed to flow should be slow at first (3 to 5 cc. per minute) but may be increased as the transfusion continues to 10 to 15 cc. per minute. The average transfusion of 500 to 600 cc. will take about an hour to run in.

Experimental Data. Before using any of this blood for transfusions, it was felt that its value and safety should be established. We found, using the Russian preservative, which consisted essentially of 0.5% sodium citrate and enough sodium chloride so that the final solution was isotonic,* that hemolysis was apparent after 3 days of storage and had become marked at the end of 10 days. In spite of the successful 2-year transfusion record of the Montreal workers, we were hesitant about using blood apparently containing considerable free hemoglobin. It was suggested to us⁷ that we experiment with the effect of sugar in the preservation of placental blood, inasmuch as the appearance of hemolysis had been found to be nearly coincidental with a sharp drop in the sugar content of preserved adult blood and could be largely prevented by the addition of glucose. It is interesting to note that, although Belenkiy¹ mentioned in 1936 that the addition of dextrose gave better preservation of blood, this method apparently has not been used until recently.^{4,7} As shown in Figure 1, blood sugar observations on

* We used Citro-Seroid, during the early part of our work, made by Ayerst, Harris, and McKenna.

placental bloods quickly demonstrated that hemolysis appeared at the same time as a sudden fall in the sugar concentration from the previous level of 20 to 40 mg. % to zero. We then ran 3 series of flasks varying the original preserving fluid by adding dextrose in amounts of 2, 3, and 4 gm. respectively, thereby making the final solution hypertonic. A second group of 4 series of flasks was done adding the dextrose as an isotonic solution so that the actual amount of sugar present per flask was 0.5, 1.15, 2.5, and 3.75 gm. respectively, thereby keeping the final solution isotonic. Blood sugars were done in each group over a period of 90 days, at first daily, later 2 or 3 times a week, and finally once a week. The sugar values corresponded within reasonable limits of error to the amount of sugar

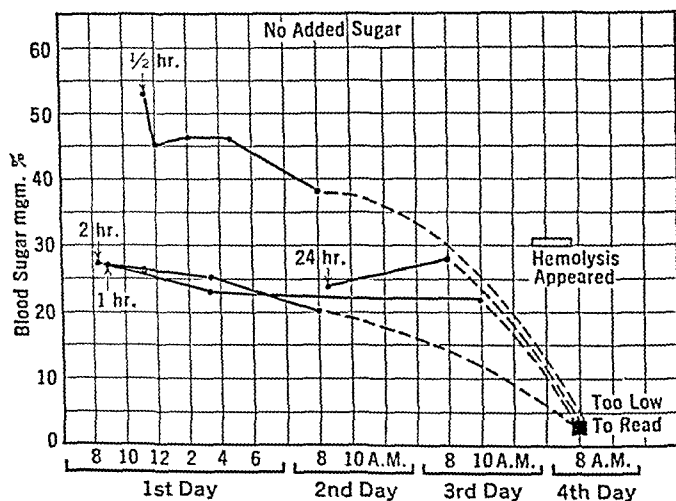


Fig. 1.—Blood sugar levels when isotonic saline and citrate (0.5%) was used as preservative. Note sudden disappearance of sugar on the fourth day.

added in each case. For instance, with 0.5 gm. of dextrose there was an average value of 240 mg. % and with 2 gm. a value of 900 to 1100 mg. %. The amount of preservative used was kept at 100 cc. per flask and the average amount of blood added was 85 cc.

It was found that there was a slow but steady drop in the sugar concentration during the period of storage with each of the series of flasks containing less than 2 gm. of dextrose. At the end of 80 to 90 days those containing 0.5 gm. of dextrose had fallen to zero, those with 1.15 gm. from 600 to 200 mg. %, but those with 2 gm. remained very nearly the same, falling only to 800 to 900 mg. %. It was only in those flasks containing 2 gm. or more of added dextrose that the maximum delay in the development of hemolysis appeared. In this group, while hemolysis became evident almost as soon as in the absence of added sugar, it progressed very slowly and did not become marked until after 8 weeks of storage. Therefore, we have used 2 gm. of dextrose per flask, because this allows as much sodium

chloride as is possible in the preserving mixture with a concentration of sugar which will give the most satisfactory preservation. Since agitation of the blood increases the speed of hemolysis and probably actually produces a greater degree, the hemolysis in these flasks was affected because frequent mixing was necessary for the blood sugars. For the same reason, we cannot compare accurately the effect of the hypertonic and isotonic solutions. This has been demonstrated by a third series using the isotonic preservative in which the flasks have not been shaken up or disturbed except for observation of the degree of hemolysis (Fig. 2). This has shown a very slow development of hemolysis, being of slight degree at the end of 1 month, moderate at the end of 2, and marked only as the blood approached 3 months of storage.

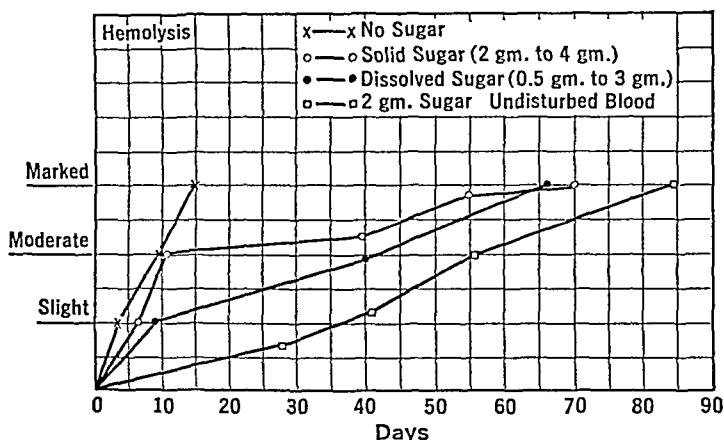


FIG. 2.—This shows the rate of development of hemolysis with various types of preserving fluid. The lowest curve, that of the undisturbed blood, shows the true effect of the addition of sugar. In the two middle curves the specimens were thoroughly mixed for the frequent sugar determinations.

In regard to the actual condition of the blood cells during the 3 months period of storage, successive stained smears at about 2-week intervals have shown that both the red and white cells remain quite normal in appearance (Fig. 3). We have also found that while the number of nucleated red cells tended to decrease, at least during the first 10 days, some of them were still present in the smear after 3 months.

A study of the red cell count and hemoglobin content was done on 67 unselected specimens as diluted by the preserving fluid (Fig. 4). The average red cell count was 2,023,000 (highest, 3,260,000; lowest, 920,000). The average hemoglobin (Haden-Hauser) was 7.4 gm. (3.75 to 11.3 gm.). The average total volume of 58 specimens was found to be 184 cc. with a range of 110 to 270 cc. In explanation of the lower volumes, it should be said that at times, before our collection technique was perfected, there was spilling of some of the 100 cc. of preserving fluid, originally placed in the collecting flask

before autoclaving, as well as poor collections of blood. The wide discrepancies that occurred in the relation of the red cell value to the volume can be accounted for partly by the above and partly by the variation known to exist in fetal blood values. Our figures for average values show that the diluted preserved placental blood is approximately equal to one-half the volume of average adult blood, but this ratio is not entirely reliable in estimating the amount of preserved blood needed for a given transfusion.

The initial experimental work was carried out with no pretense of sterility in handling the flasks of blood, in fact we did not even use sterile pipettes to withdraw the samples of blood. This was done because we did not then care whether or not these flasks remained sterile. We were curious to see how easily they might be contaminated. A total of 69 flasks were cultured from 1 to 4 times and 11 of these (Table 1) showed bacterial growth. In 8 instances the organ-

TABLE 1.—BACTERIOLOGY DURING EXPERIMENTAL PROCEDURES.

Number of specimens cultured	69
Begun in broth	71
Begun on blood agar plates	10
Begun by incubation of specimen	42
Total cultures made	123
Number showing growth	11
<i>Bacillus subtilis</i>	4
<i>Staphylococcus albus</i>	1
Hemolytic <i>Staphylococcus aureus</i>	1
Diphtheroid bacillus	1
Non-hemolytic streptococcus*	2
<i>Bacillus coli</i> *	2

* The *B. coli* and one of the streptococci were obtained in the only 3 instances of collection in a breech delivery.

isms were thought to be laboratory contaminants; in the remaining 3 which were breech deliveries, *B. coli* was found in 2 and the other may have been contaminated either at the time of collection or subsequently in the laboratory. With the exception of *B. coli*, the organisms listed in the table are common laboratory contaminants. In 4 other instances in which bacterial growth was found subsequent cultures were sterile.

Recently, we have begun culturing previously unopened flasks of blood after periods of storage varying from 6 to 90 days. At present, we have a total of 55 consecutive specimens all of which have been sterile (Table 2). These were cultured by incubation of 50 to 60 cc. of the preserved blood which was then plated on blood agar.

TABLE 2.—BACTERIOLOGY OF PREVIOUSLY UNOPENED SPECIMENS.

Number of consecutive collections cultured	55
Number showing bacterial growth	None

The collection of the blood involved only the third stage of labor. It was, therefore, necessary to prove that the mother was not harmed. We took two series of 86 cases each and compared the elapsed time of this stage of labor. In each series the mechanism was conducted

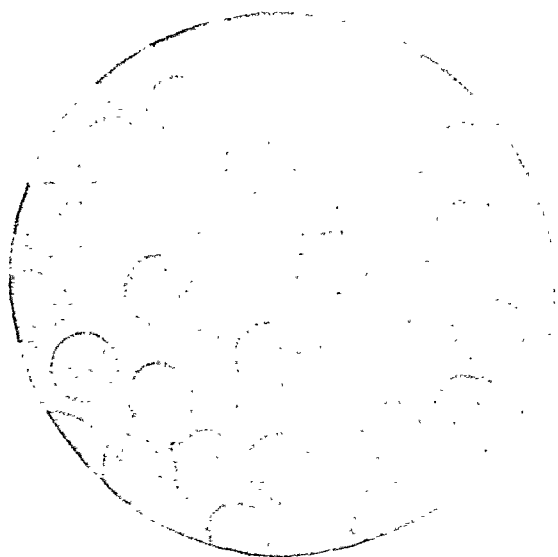
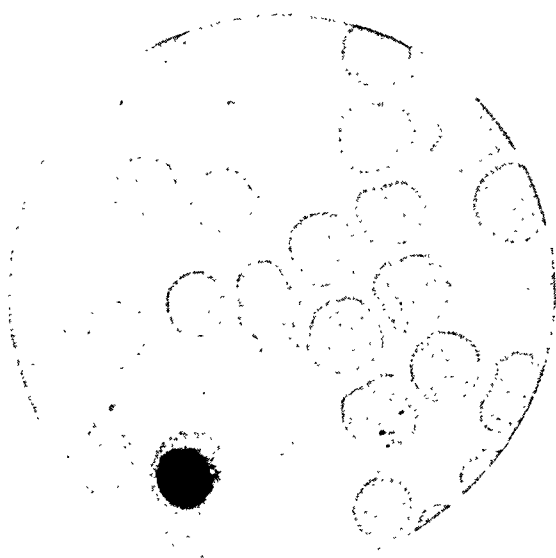


FIG. 3.—Two fields in a stained smear made from a flask containing blood which had been stored for 3 months. Note the nucleated red cell and the normal, well preserved appearance of the cells. ($\times 1200$.)

in the same manner. The cases where the cord and placenta were emptied of their blood took 8 minutes 5 $\frac{2}{3}$ seconds for completion of the third stage. The cases where the cord and placenta were allowed to remain intact required 8 minutes and 5 seconds.

Comment. We feel that our present technique of collecting and storage is a safe, satisfactory, and efficient method of obtaining blood for transfusions.

We have shown that the labor mechanism of the patient from whom the blood is collected is not affected. Therefore, the procedure is not harmful to her.

While the cord Wassermann test has been shown to be unreliable as an absolute diagnostic criterion of congenital syphilis,^{3,12,13} and therefore not done by some authors,¹⁰ we add it to our precautionary measures as a further safeguard. The same fault can be found with

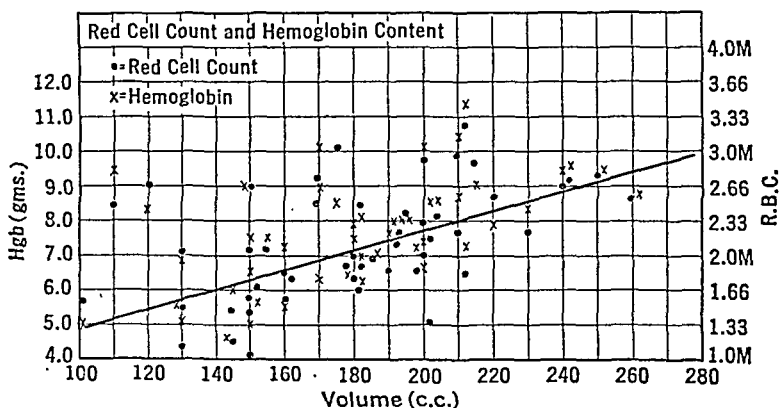


FIG. 4.—The red cell count and hemoglobin content of each specimen is plotted according to the volume. They tend to increase directly with the volume as indicated by the solid line representing the mean values.

most if not all of our serologic tests in adults. The literature contains many reports of false positive as well as false negative results during pregnancy. As long as the blood tests for the presence of syphilis are not absolutely reliable, we feel it is wise to take all reasonable care to exclude the possibility of transmitting this disease.

Further experimentation is being carried out with the preserving fluid, regarding its physical and chemical properties and the amount necessary to use. The addition of saline and glucose to the blood in the quantities used, gives a reasonably satisfactory preserving effect and, in most if not in all instances, this would add to the beneficial effect of the blood and certainly would not be harmful to the patient.

Several of the Russian workers^{2,14,15,17} have used a citrate solution, as in the ordinary citrate transfusion, as the preservative. It is also used in this country as mentioned in the reports of Fantus and Scheimer,⁶ and Grodberg and Carey.¹⁰ Goodall⁹ has used citroseroid in his work. We began a year ago with citroseroid but, as we have shown, obtained much better results with the addition of

dextrose. Karavanov¹¹ and Belenkiy¹, as far as we know, were the first to use the saline-citrate and dextrose-citrate preserving mixtures. DeGowin *et al.*⁴ have just reported that preservation of adult blood is much more satisfactory with the addition of dextrose and feel that anaerobic storage will further improve preservation.

While we feel that our technique satisfactorily insures sterile preserved blood, the possibility of contamination with a pathogenic organism at the time of collection is, of course, always present. However, this is just as true in any other method of collecting blood for transfusion. If contamination should occur in the case of this preserved blood, one of two things would be true after the required 10-day period of storage. Either the organism would be so attenuated as to be non-pathogenic, or the change in the condition and appearance of the blood at this time, as previously stated, would at once indicate the presence of bacterial growth. We have not had the opportunity to observe this in our present series of cultures except for the collections from breech deliveries. Syphilis and other contagious diseases, significant abnormal findings in the mother, and blood dyscrasias or other diseases in the infants, are ruled out in the obstetric work-up of the cases used and the follow-up of the baby during the 10-day period of storage.

For most transfusions it is necessary to use two or more flasks of blood, and, we have in some cases, cross-matched the flasks used against each other as well as against the patient. We have never found any incompatibilities between flasks containing bloods of the same group, and have not felt it necessary to continue this additional cross-matching. We have given 18 transfusions to date without a severe or serious reaction. We did have in one of our first transfusions a mild reaction, consisting of a short chill and fever of 100°. This appeared an hour after the transfusion was finished and was not accompanied by urinary findings or other evidence of incompatibility of the blood. This transfusion was given quite rapidly and it may be considered a so-called "speed reaction"⁵ or possibly due to pyrogen contamination. Both the Russian and American workers, using simple citrated blood,^{2,6,14,15,17} have almost universally found that 10 to 12 days is the maximum period that the blood can be preserved in good condition. The Boston workers,¹⁰ however, report a maximum of 30 days storage before use. It has long been felt that citrated blood could not be preserved more than a few days, at most, without the probability of deterioration of a degree sufficient to affect its safety and value for transfusions. Most of the reports of preserved citrated blood give a high percentage of reactions, some as high as 67%.¹¹ We have not enough data at present to verify our impression that these may be due to this method of preservation. However, Goodall⁸ has had 2 years' experience using citro-seroid for preservation and has not had reactions following transfusions. We feel that the type of preservative may

be responsible for this record. Our method maintains the blood in a more perfect state of preservation and permits a longer period of storage than citro-seroid. The blood we have used for transfusing patients has been stored for periods of 10 to 50 days, and most of it has been between 20 and 35 days old.

Table 3 shows the data concerning the transfusions we have given. We realize that the number is too small to justify any definite conclusions concerning the value of this blood as compared to that of fresh blood. However, these observations support our contention that the preserved blood is approximately as effective as fresh adult blood for transfusion purposes. In every case we have noticed the clinical improvement which one expects to see following the average successful transfusion. The patients have been observed carefully for any evidence of reaction to the preserved blood and but one instance has occurred, as previously mentioned. In no case has the urine shown any evidence of hematuria, nor has there been any clinical jaundice except in the case with hemolytic anemia, where it was present prior to the transfusion. The red count and hemoglobin have shown a fairly satisfactory increase in most instances. In transfusions 1, 11, 14, 15, 16, and 17 (3 cases) the presence of either dehydration, severe infection, or an active hemolytic process was perhaps responsible for the failure of the red cell values to rise. In 3 cases (4, 12, and 13) we did not obtain satisfactory counts for comparison. Our results with these 18 transfusions, we believe, show that the preserved red blood cells can be maintained for a period of at least 50 days, and probably longer, in a condition which permits them to again take up their original function in the blood stream. This has been evidenced in our series by the gain in the red count and hemoglobin values over a period of 12 days after transfusion. At the end of this time, the patients had either been given another transfusion or discharged from the hospital making a longer follow-up impossible. We have found no evidence that these preserved cells tend to disappear rapidly from the recipient's circulation, nor that the use of this blood is in any way detrimental to the recipient. However, the contention that it is just as good as fresh blood is not tenable for there are well known facts, such as the rapid disappearance of complement and loss of the property of coagulation which at once refute it.

The amount of preserved blood used at one time has varied from 125 cc. in a child to 1000 cc. in an adult who had a severe hemolytic anemia. Five to six hundred cc. is the average amount used, and, in our short experience, seems to be the approximate equivalent in effectiveness of the average transfusion of 400 to 500 cc. of undiluted citrated adult blood. This blood has been used in the treatment of shock, hemorrhage, infection, and anemia with good results. One of the most important features of the preserved blood is that it is always on hand in an emergency, and it is possible to have the

TABLE 3.—TRANSFUSIONS GIVEN WITH PRESERVED BLOOD.

Transfusions.	Diagnosis.	Before transfusion.			Transfusion.		Flasks used.		After transfusion.			Remarks.
		Date.	R.B.C. (mill. per c.mm.).	Hgb.* (%).	Amt. of blood given (cc.).	Date.	No.	Age in days.	Date.	R.B.C. (mill. per c.mm.).	Hgb.* (%).	
1	Prolonged labor with shock and dehydration	9/14	3.7	75	325	9/14	2	14 21	9/15	3.2	68	Rapid relief of shock.
2	Abruptio placentæ with hemorrhage and shock	9/22	3.1	45	595	9/22	3	17 18 30	9/29	3.3	49	Rapid relief of shock.
3	Placenta previa marginalis with hemorrhage and shock	10/15	2.2	45	475	10/15	3	20 21 21	10/24	3.6	55	Rapid relief of shock.
4	Postpartum bleeding with shock	475	10/9	3	26 31 33	10/10	3.3	52	Rapid relief of shock. (? of speed reaction.)
5		10/14	2.2	23	355	10/16	3	23 26 30	10/18	2.3	26	
6	Premature delivery; acute pyelitis; anemia	10/22	2.6	31	480	10/23	3	29 30 30	10/24	3.0	42	Steady rise in r.b.c. and hgb. Infection subsided after delivery.
7		10/25	3.5	45	455	10/27	3	26 29 34	10/28	4.1	49	
8	Ovarian cyst; chronic pelvic inflammatory disease; postoperative anemia	11/25	2.8	62	360	11/26	3	10 31 44	11/28 12/2	3.8 3.9	71 78	Good response.

9	Chronic lung abscess; anemia	11/18	3.8	58	620	11/19	3	10 20 24	11/20 11/23	3.7 4.1	65 65	Fair response.
10	Postoperative anemia and wound infection	11/28	3.3	65	600	11/29	3	10 27 50	11/30 12/1	3.7 4.1	75 81	Good response.
11	Acute hemolytic anemia (sulphanilamide)	1/2 1/4 1/5	5.0 2.5 1.8 (50)?	1000	1/5	6	21 21 23 24 26 27	1/6	1.8	..	No apparent response. However, after 500 cc. fresh blood on 1/6, r.b.c. was 1.3 mill., showing continued blood destruction.
12	Ruptured ectopic pregnancy with shock (about 1 pint of blood in abdomen)	2/12	(4.0)?	55	505	2/12	3	22 30 49	2/13	4.0	80	Good response. Relief of shock.
13	Postoperative shock	375	1/30	2	39 46	Rapid relief of shock.
14		2/17	4.0	85	225	2/18	1	30	2/20	4.0	68	Patient critically ill. Good clinical response. 500 cc. fresh blood given 2/28 with only a transient effect.
15	Ruptured appendix; general peritonitis, empyema and pneumonia	2/20	4.0	68	160	2/21	1	56	2/22	3.5	58	
16		2/22	3.5	58	190	2/22	1	31	
17		175	2/25	1	36	2/26 2/28	2.0 2.2	39 42	
18	Puerperal sepsis; pelvic abscess; B. hem. strep. infection with chills and fever	2/22	3.1	52	465	2/22	3	15 15 11	2/25	3.5	62	Good result.

There was no hematuric jaundice or unfavorable reaction except that Case 4 had a chill, 15 min., rectal temperature 101° F., and Case 11 had a marked gross hematuria from the day before to 2 days after transfusion and a deep red colored serum.

* Haden-Hauser, rarely Tallqvist.

transfusion in progress within less than 1 hour after being notified that blood is wanted.

Conclusions. 1. Following the procedures as described by us, any obstetric department may collect placental blood without interference with its normal routine or technique.

2. The blood may be collected without harm to the mother.

3. An isotonic solution of 0.5% sodium citrate, 4.6 gm. sodium chloride, and 2 gm. of dextrose per 100 cc. will satisfactorily preserve the blood for a period of 8 to 10 weeks in a condition suitable for transfusion use.

4. This method will provide an important source of blood which can be made constantly available for transfusion purposes.

5. We foresee an especial value in emergency transfusions because it takes less than 1 hour to group, cross-match, prepare the blood, and begin the transfusion under all reasonable circumstances.

6. The preserved placental blood is without danger from bacterial infection including syphilis, and it conforms to the New York State requirements for blood donors.

7. It is a safe and efficient form of blood for use in transfusing patients.

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BLOOD STUDIES ON THE NEWBORN.

I. DETERMINATION OF HEMOGLOBIN, VOLUME OF PACKED RED CELLS, RETICULOCYTES, AND FRAGILITY OF THE ERYTHROCYTES OVER A NINE-DAY PERIOD.

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For more than 100 years blood studies on the newborn have furnished an interesting and at the same time contradictory chap-

ter in hematology. It has been widely accepted that increased values for hemoglobin, erythrocytes, volume of packed red cells, bilirubin and so on, are to be encountered in the blood of newborn infants,^{25b, 32, 58b} although there are many reported instances where these high levels have not been substantiated. Investigations on the fragility of the red cells have led to considerable confusion, so that no definite picture of the situation has ever been accepted. It was this unsettled state of knowledge concerning fragility which led us to undertake the present study. We approached the problem, not so much to prove or disprove previous contributions, but rather to find what could be uncovered in the light of present-day methods, with special reference to the Evelyn photoelectric colorimeter^{9, 10} and the hemolytic index.⁵⁴ We shall confine ourselves in this paper to studies of the hemoglobin, volume of packed red cells and fragility of the red blood corpuscles, with brief notes on the reticulocytes; and later take up our findings in regard to the direct and indirect blood bilirubin in the infant, with discussion of icterus neonatorum and of several cases of erythroblastosis.

Without reviewing the literature completely, we find it desirable to include under the appropriate headings some of the more outstanding and contributory works of the past and present. It is interesting to note that as early as 1831, according to Bayer,⁴ Denis first published figures on the blood of newborns. Later, in 1866, Kruger²⁹ observed that at birth the amount of hemoglobin in the blood of a newborn infant was equal to that of the mother, only to rise to a higher figure later. Then in 1878 Leichtenstern³¹ pointed out that age and sex of the infant should be taken into consideration before drawing conclusions as to the normal levels, but others since have shown the differences to be negligible in the first few days of life. Schiff⁴⁵ in 1892 demonstrated that differences in values may be due to environment and geographic location. The exhaustive study of Williamson⁵⁷ in 1916 reported some of the highest hemoglobin values on record, probably due to the spectrophotometric method employed. This made a historic contribution to hematology and pediatrics. His work, using 16.9 gm. hemoglobin equivalent to 100%, is the only standardized investigation prior to 1924. Unfortunately, the early workers and many of the later ones, failed to state on what basis their values were made, so that a complete comparison is difficult, if not impossible. For example, some investigators, using the Haldane and Van Slyke methods, employed 13.8 gm. hemoglobin per 100 cc. blood as equivalent to 100%, while others used 17.2 gm., and so on. Others merely reported in

terms of percentage of normal standard means little when taken alone, we do feel, as did Haden and Neff,¹⁹ that for the sake of comparison results should be expressed in percentages of a standard as well as in grams per 100 cc. Many workers have not given the dispersion of values from minimum to maximum, but have

been content to state the average figure for a series. This confuses the picture considerably and we feel this should be kept in mind when comparing results.

We shall not enter into a detailed discussion of the physiology of the newborn, into the anemias, diseases or theoretical problems of the infant, but will merely present our material as we found it in Montreal, offering such conclusions as we feel are justifiable.

Material. Normal, full-term white infants born on the wards of the Montreal Maternity unit of the Royal Victoria Hospital were taken for study, excluding from the series only those in whom serious illness or complications developed or on whom determinations were too incomplete to be of value. Several cases of erythroblastosis were taken as they occurred but are not included in the general findings. These will be taken up separately. We limited our study and survey of the newborns to a 9-day period, making determinations on the first (day of birth), second, fourth, sixth and ninth days. No attempt is anticipated to follow these infants later in the out-patient department. In all, we examined 65 newborns during the period of study, obtaining 5 complete studies on 29, 4 out of 5 on 12, and 3 or less on the remainder, with 5 of these disqualified due to illness or transfer. The newborns in the series were observed closely on the wards in order to detect the occurrence of icterus neonatorum, erythroblastosis, complications, and so on. The blood on the first day was obtained immediately from the umbilical cord, usually after cessation of pulsations at the time of delivery, placed in especially prepared vials containing 10 mg. of potassium (4 mg.) and ammonium (6 mg.) oxalate per 5 cc. blood, and sent directly to the laboratory. The bloods thereafter were obtained from the sagittal sinus by fontanel puncture, under the personal supervision of one of us, so that a constant quantity was obtained in the same manner and sent to the laboratory in the special vials. Determinations were made at once, or within a few hours of the time of withdrawal, for it has been known for some time that cord blood may readily hemolyze in oxalate or citrate solutions.^{15,40}

Technique. Throughout this study, with the exception of the determinations of volume of packed red cells and reticulocytes, the Evelyn photoelectric colorimeter^{9,10} was used. The colorimeter is a stabilized, direct-reading, single-photocell, photoelectric colorimeter which is equipped with light filters. Extensive and exhaustive usage and testing of the machine by Evelyn and coworkers have proved the value and accuracy of the apparatus, and we are indebted to him for his instructions and helpful suggestions. We employ this machine regularly for routine hemograms in the Pathological Institute, so that we feel we have a great familiarity with it. The colorimeter is also regularly employed in the laboratories of the Royal Victoria Hospital, the McGill University Clinic, and in other medical centers of the East.

For the hemoglobin determinations, a calibrated 0.05-cc. pipette was used to measure the blood, which was in turn added to 25 cc. distilled water in a standard colorimeter tube. A drop of concentrated ammonia water was added to insure complete and immediate hemolysis and the tube was placed in the machine and the hemoglobin read directly, using the filter which has a maximum transmission of 540 millimicrons. It has been previously found by one of us (Waugh) that a blood in which there are 5 million erythrocytes of normal size (95 cu. μ) and containing a normal amount of hemoglobin (hemoglobin concentration of 1) has 15.6 gm. of hemoglobin per 100 cc. of blood. This figure was determined by the Van Slyke method for oxygen capacity. This value is taken as 100%, and,

as may be readily seen, is preferable as a standard to any figure based upon simple estimations of total hemoglobin in normal individuals, which is subject to great geographic influences and other variables. We shall employ this value as our standard and as a base line for determining the differences seen in the blood of newborn infants. Foster and Johnson,¹¹ Haden¹⁸ and Osgood⁴⁰ also found 15.6 to 15.8 gm. per 100 cc. to be standard (equivalent to 100%) for adults in their respective areas.

The regulation Wintrobe hematocrit tube^{58d} filled with 1 cc. of whole blood was used for determining the volume of packed red cells. The determinations were made in duplicate and centrifuged for $\frac{1}{2}$ hour at 3000 r.p.m. in a Type C International centrifuge. These results are expressed in percentage. We have found, using the anticoagulant which we employ, that the blood of an adult in which there are 5 million erythrocytes of normal size has a volume of packed red cells of 47.5% (Wintrobe^{58d}). This value we take as our standard for comparisons. The reticulocytes were counted by the approved method, using the vital staining technique with brilliant cresyl blue, and counting the number of young forms per 1000 red cells. These counts were not made on all cases but on a sufficient number to be of some significance.

The fragility of the erythrocytes was determined by the methods developed first by Waugh and Chase⁵⁵ and later modified by Waugh and Asherman.⁵⁴ These methods provide for the use of Simmel's solution rather than isotonic sodium chloride, and now utilize the Evelyn colorimeter so that the degree of hemolysis can be calculated directly from the amount of hemoglobin liberated rather than by the tedious and variable procedures with enumeration of the red cells heretofore used. The reader is referred to the above papers for the preparation of the solutions and detailed technique. The pH of the solutions was carefully maintained at 7.1, as recommended by the authors, and was diluted and distributed into liter bottles labelled 100, 70, 65, 60, 55, 45, 40, 35, 30, indicating the percentage of the original solution. The blood was withdrawn and measured with a calibrated 0.02-cc. pipette and added to 10 cc. of each of the solutions in a standard colorimeter tube. The contents were mixed gently, the tubes centrifuged for 10 minutes at a low rate, then placed in the colorimeter and the amount of hemoglobin liberated read directly. From these readings the percentage of hemolysis (proportion of hemoglobin liberated to total hemoglobin) and an index of hemolysis, which is the sum of the percentages of hemolysis of all the tubes, are used to express the resistance of the cells to the solutions. Waugh and Asherman have found in examining the blood of healthy adults that the average index of hemolysis is 400, with a maximum normal resistance of 350 and a minimum of 450. It has been found that in obstructive jaundice of long duration the index falls to approximately 250, while in hemolytic jaundice it rises to the neighborhood of 650. The use of this index is advocated "as it offers a much readier and more precise means of expressing and recording the fragility of the red blood cells."

Hemoglobin. Literature. We shall not outline the literature prior to 1920, but shall mention only the more outstanding work since that time. Lucas *et al.*,³³ using the Palmer-Robschheit method, found 36 bloods on the first day averaged 117% (85 to 140%); 27 on the second, 114% (100 to 135%); 17 on the third, 110% (80 to 135%); 26 on the fourth, 114% (80 to 130%); 18 on the fifth, 107% (75 to 125%); 21 on the sixth, 113% (80 to 130%); 16 on the seventh, 109% (75 to 125%); 20 on the eighth, 103% (60 to 125%); and 17 on the ninth, 103% (90 to 115%). No standard

for their work is stated. They observed that sinus blood gave slightly higher readings than peripheral blood, although the differences were almost negligible, and that the hemoglobin averages of infants with icterus neonatorum were not reduced. In contrast to Schiff,⁴⁵ they found that tying the cord before and after cessation of pulsation had no effect on the hemoglobin after birth. Haden and Neff,¹⁹ in a standardized study in which they took 15.6 gm. hemoglobin per 100 cc. of whole blood as 100%, used the ferricyanide method of Haldane and Van Slyke and venous blood. They found one 11-hour blood was 15.6 gm., 3 5-day bloods were 17.8, 16.2, 20.1 gm., one 6-day blood was 18.8 gm., one 8-day blood was 16.4 gm., and three 9-day bloods were 18.5, 19.2, 16.6 gm. Then Börner,⁵ using the Huefner spectrophotometer and Bürker hemoglobinometer, studied 30 cases over a period ranging from 25 minutes to 15 days and obtained a distribution of hemoglobins from 15.2 to 23.71 gm., 22 of the cases having values above 18 gm.

Mitchell^{38b} studied 69 cases and found that practically all infants showed a reduction in red cells and hemoglobin between the first and tenth days. He obtained hemoglobin averages of 120% (89 to 152%) on the first day, 114% (87 to 154%) on the third, 111% (76 to 148%) on the seventh and 106% (74 to 138%) on the tenth day. The blood values of both jaundiced and non-jaundiced infants fell to the same figure, although the total fall of the former was slightly greater. This was held by the author to be negligible. All other things being equal, he found that relative changes in weight exert an effect on the loss in red cells and hemoglobin. Mackay^{34a,b} reported hemoglobin values of approximately 100% for infants during the first month, but later revised her values and reported 143% under 24 hours with a fall to 130% by the eighth day. She attributed the rapid fall to excessive destruction of the red cells. She observed that hemoglobin values are inversely proportional to the birth weights.^{34b,c} Goldbloom and Gottlieb^{15b} found the high hemoglobin level of the newborn to be related to the low oxygen tension of the blood of the fetus *in utero*, and using guinea-pigs showed that increasing the oxygen tension lowered the red count and caused a rise in blood bilirubin. This they thought to be due to a compensatory increased destruction of erythrocytes. Whitby and Hynes⁵⁶ found a mean of 151% at birth (range, 130 to 162%). Mugrage and Andresen,³⁹ using 13.8 gm. as standard, found 17.14 gm. for 40 newborns (range, 13.6 to 20.2 gm.) and a coefficient of variation of 8.6%. They found the differences between male and female infants to be negligible at this age. Andersen and Ortman¹ found 17.44 gm. of hemoglobin in the newborn (range, 12.7 to 24.85 gm.), using the Hellige universal colorimeter and 13.8 gm. as a standard. They also observed that a greater variability of values existed in infants as compared with adults. Guest, Brown and Wing¹⁷ reported a hemoglobin average of 17.9 gm. for 24 samples

of cord blood, with a dispersion of 13 to 22 gm. They obtained a 1- to 10-day average for 89 cases of 19 gm., with a range of 14.5 to 25 gm. They utilized the Palmer carbon monoxide hemoglobin method, modified with a Wratten filter No. 74. Ross, Waugh and Malloy⁴² found that in 7 cases the blood on the first day averaged 110% while by the fifth day these same infants showed 90% hemoglobin. Another series of 41 cases on the fifth day averaged 109% (Palmer method).

Observations. Using the Evelyn photoelectric technique and considering 15.6 gm. hemoglobin per 100 cc. blood as equivalent to 100%, we obtained an average hemoglobin of 15.36 gm. in 52 umbilical bloods with a dispersement of 11.86 to 18.72 gm. On the second day, 45 samples from the fontanel averaged 15.49 gm. (range, 11.23 to 19.66 gm.). On the fourth day, the average of 46 infants was 15.46 gm. (range, 11.86 to 19.34 gm.). By the sixth day, the average of 39 samples was 14.93 gm. (range, 11.86 to 18.72 gm.). On the ninth day the average of 39 cases was 14.70 gm. (range, 11.86 to 17.94 gm.). In order to determine whether the presence of anemic infants had materially changed the general averages, we broke down our data into 20% with the highest hemoglobins, the 20% with the lowest hemoglobins, and the intermediate 60% and compared them with the averages for all cases. It is readily seen (Table 1) that the 60% group is nearly identical with the average of all cases, so that no definite influence by a minority of low readings is exercised.

TABLE 1.—HEMOGLOBIN AVERAGES OF ALL CASES COMPARED WITH THE SELECTED GROUPS. GRAMS/100 CC. BLOOD.

Time.	No. of cases.	Averages all cases.	Averages 20% high.	Averages 60% mid.	Averages 20% low.
Cord blood	52	15.36	17.02	15.37	13.70
2d day	45	15.49	18.11	15.30	13.45
4th day	46	15.46	17.74	15.37	13.51
6th day	39	14.93	17.11	14.88	12.87
9th day	39	14.70	16.95	14.66	12.73

In our series, 30% of the infants developed clinical icterus. Of these 18 newborns, all but 5 developed jaundice on the fourth day. The others became jaundiced on the second, third and fifth days. The average hemoglobin of 16 cord bloods of infants who later developed jaundice was 15.07 gm., while the remaining non-icteric infants averaged 15.49 gm. The 15 samples from the second-day bloods on babies who later developed jaundice gave an average hemoglobin of 15.4 gm. with the non-icteric infants averaging 15.54 gm. On the fourth day, on which the majority became obviously icteric, 14 jaundiced infants averaged 15.3 gm., as against the 15.52 of the non-jaundiced group. By the sixth day, 13 icteric infants averaged 14.5 gm. and the non-icteric 15.13 gm. On the ninth day, 13 icteric infants averaged 14.35 gm. with the non-icteric at 14.85 gm. It will be seen that the greatest differences occur

after the fourth day, although the entire icteric group present a slightly lower hemoglobin average than do the non-icteric. The difference is, however, almost negligible and no correlation could be made between individual values and the appearance of jaundice. Table 2 is a comparison of data on jaundiced and non-jaundiced infants. The cord blood hemoglobin of a case of erythroblastosis was 11.86 gm., dropping to 11.23 gm. on the second, 10.78 gm. on the fourth, and 10.3 gm. on the sixth days. Another case on the third day had a hemoglobin of 8.4 gm., while one studied on the fourth day showed a value of 9.83 gm.

TABLE 2.—A COMPARISON OF HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY AVERAGES BETWEEN JAUNDICED AND NON-JAUNDICED INFANTS. (NUMBER OF CASES AVERAGED IN PARENTHESES.)

Time.	Hemoglobin, gm. per 100 cc.		Vol. packed red cells in percentage.		Index of fragility.	
	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.
Cord blood	15.49 (36)	15.07 (16)	51.4 (35)	51.1 (16)	405 (36)	390 (16)
2d day	15.54 (30)	15.40 (15)	49.8 (30)	48.8 (15)	350 (30)	338 (15)
4th day	15.52 (32)	15.30 (14)	49.2 (32)	47.7 (14)	324 (32)	335 (14)
6th day	15.13 (26)	14.50 (13)	47.7 (26)	45.1 (13)	333 (26)	346 (13)
9th day	14.85 (26)	14.35 (13)	46.5 (26)	44.4 (13)	344 (25)	379 (12)

In summarizing our findings on over 200 hemoglobin determinations on infants during the first 9 days of life, it is obvious that our results in no way agree with the extremely high figures which have been reported in the literature. There are, of course, several points which have to be borne in mind in this connection: first, the lack of definite data in many of the previous communications on the standards employed, making a true comparison difficult. Our determinations were all made in duplicate and read directly from the Evelyn colorimeter, which is known to be accurate to within $\pm 2\%$, and reported in grams per 100 cc. whole blood. Secondly, there is the possibility of differences due to various geographic locations, for, as is well recognized today, this latter factor plays an important rôle in determining so-called normal figures for hemoglobin in adults and infants. In this connection, seasonal and climactic factors may be held partially accountable, for Wintrobe,^{58b} in an extensive review, has pointed out that lower values are met with in the northern, colder regions. Our series of cases were all healthy, full-term infants of average birth weight, born between August 15 and October 1, but we did not follow the weight changes during the period of study. Nevertheless, it would appear that while there is an average variation from approximately 14 to 17 gm. (individual variation from about 11.5 to 19.5 gm.) of hemoglobin per 100 cc. of blood, the vast majority of children in Montreal are

born at this time with very close to 15.6 gm. of hemoglobin or 100%. Similar values are met with in blood taken from the fontanel on the second and fourth days.

During the 9-day period there occurs a gradual fall in the hemoglobin, which is equivalent to about 0.66 gm. or between 4 and 5% of the original total. This change is not noticeable until the fourth day, after which there is a definite decline, while an actual slight rise is noted on the second day. How great a rôle alterations in water content have to do with these changes is, of course, difficult to determine. The relation of hemoglobin to volume of packed red cells will be taken up in the next section with notes on probable influences. In inspecting the results of the individual infant, it was noted that some showed a constant hemoglobin level or slight rise, some showed a rather precipitous fall, while others (the majority) showed a delayed, slightly variable but constantly gradual decline in hemoglobin during the 9 days' period of study.

Table 2 clearly demonstrates that there is little, if any, appreciable difference between the hemoglobin figures of infants developing, and those not developing jaundice. Individually no relationship was found to exist between the total change in hemoglobin during the period studied and the appearance of clinical icterus. In our series, however, the babies with jaundice ran on the average a slightly lower figure with a slightly greater fall, but this difference would by no means appear sufficient to explain the jaundice on a basis of excessive blood destruction alone. Ross, Waugh and Malloy⁴² have shown that such destruction is not the cause but probably that inadequate liver function is the main factor. Moreover, as will be shown later, no relation could be demonstrated in our series between the original height or the degree of fall in hemoglobin in relation to fragility of the red cells to hypotonic solutions. It is interesting that in the cases which developed icterus gravis neonatorum, due to erythroblastosis, the figures for hemoglobin were distinctly low from the first cord blood, which substantiates the view that the hemolytic process is well under way before delivery occurs.

Volume of Packed Red Cells. *Literature.* Wintrobe^{58a} has emphasized the importance of using actual cell volume rather than the diameter of the cells, which have a variable thickness. This fact has been widely recognized and appreciated, so that the hematocrit has come into common use and further calculations concerning the cell have been derived from it.^{58a, c-e} Mugrage and Andresen³⁹ reported an average of 53.18% (44 to 63.5%) for 40 newborn infants, with a coefficient of variation of 8.8%. They found the differences between male and female infants to be unimportant at this early age. Guest and Brown¹⁶ reported 8 samples of cord blood and found a distribution of 42.9 to 69.1%. Ross, Waugh and Malloy⁴² reported 7 normal non-icteric infants with a first day average of

58% and a fifth day average of 52%. Averages for 5 jaundiced babies were 59% on the first and 53% on the fifth days. Of 41 infants at 4 and 5 days who were not jaundiced, the average volume was 52%, while the average of a group of 22 jaundiced infants of the same age was 52.5%. Andersen and Ortman¹ studied 38 cases and obtained an average of 56.5% (42 to 78.5%) and a coefficient of variation of 14.78%.

Observations. In our series, the average volume of packed red cells for 51 umbilical bloods was 51.3% (range, 41 to 61%). On the second day fontanel blood the average volume for 45 samples was 49.15% (range, 37.5 to 62%). On the fourth day, the average of 46 samples was 48.7% (range, 35 to 63.5%). By the sixth day, the average of 39 samples was 46.8% (range, 36 to 60.5%). On the ninth day the averages of bloods from 39 infants was 45.9% (range, 35 to 57%). Again, in order to determine whether a few low values were greatly influencing the general averages, we calculated the averages for the 20% with the highest readings, the 20% with the lowest readings and the 60% intermediate (Table 3). It will be seen that the averages for all cases agree very closely with the values for the 60% intermediate group, so that we feel the frankly low values are to be expected and that they do not exert an untoward effect on our general data. It appears that at birth there is an average range in volume of packed red cells of approximately 45 to 58% (individual variation from about 35 to 64%), and that the average infant in Montreal is born with a volume of about 51%, or 8% greater than the normal adult figure.

As before, we grouped our infants into those with and those without jaundice and traced the changes in volume of red cells (Table 2). The 16 cord bloods of infants who later developed jaundice averaged 51.1%, while the non-icteric group averaged 51.4%. On the second-day venous bloods obtained by fontanel puncture, the 15 who developed icterus averaged 48.5%, as against the non-jaundiced group who averaged 49.8%. On the fourth day, the icteric group of 14 averaged 47.7% and the others 49.2%. This was the day on which the majority of infants became clinically jaundiced. On the sixth day, the 13 jaundiced babies showed an average volume of 45.1% and the non-jaundiced 47.7%. On the ninth day, the 13 jaundiced infants averaged 44.4% and the non-jaundiced 46.5%. Here again, the most obvious change occurs after the fourth day when icterus appears. We were unable, however, to observe any correlation between the original height and subsequent changes of individual values and the appearance of clinical jaundice. The case of erythroblastosis on which umbilical blood was obtained gave a volume of 37.2%, while on the second day it dropped to 34%, on the fourth day to 34% and on the sixth day to 30.5%. A third day sample of another case was 23.5%, while 1 fourth day case gave a value of 32%.

It is evident that our results are similar to those reported in the literature, although here again we are slightly lower in our averages. As clearly seen in Table 3, however, our figures are not influenced

TABLE 3.—VOLUME OF PACKED RED CELLS OF ALL CASES COMPARED WITH THE SELECTED GROUPS. (EXPRESSED IN PERCENTAGE.)

Time.	No. of cases.	Averages, all cases.	Averages, 20% high.	Averages, 60% mid.	Averages, 20% low.
Cord blood	51	51.3	58.1	51.1	45.1
2d day	45	49.5	58.0	49.2	41.7
4th day	46	48.7	56.4	48.5	41.9
6th day	39	46.8	55.1	46.7	38.8
9th day	39	45.9	53.1	45.9	38.5

by anemic infants and we feel these results to be a true picture for this locality. They are also in keeping with our hemoglobin values. However, in contradistinction to the delayed drop in hemoglobin which does not appear until after the fourth day, there is a continuous fall in the volume of packed red cells from the first day. This brings up the question of mean corpuscular hemoglobin concentration. If this is computed from the averages of all cases for each day it is found as follows: cord blood 30%, second day 31.3%, fourth day 31.8%, sixth day 31.9%, and ninth day 32%. It should be borne in mind that we are using 15.6 gm. of hemoglobin as normal for 47.5% volume of packed red cells and therefore 33% is our normal mean corpuscular hemoglobin concentration for adults (Wintrobe^{58a}). It is quite apparent therefore that there occurs during this period a rise in hemoglobin concentration toward that met with in the adult. Guest, Brown and Wing¹⁷ reported an increase in hemoglobin concentration after birth, while others have found the concentration constant throughout and to be similar to that met with in the adult.

It is obvious that several factors can and do play a rôle in the reduction of the volume of packed red cells without proportional reduction in hemoglobin. It is difficult, of course, to tell which plays the greater part and how much they may make closer correlation of both impossible due to their interrelationship and our insufficient understanding of them. Loss of fluid from the cells could account for the fall in volume without a corresponding fall in hemoglobin, and we believe this to be quite possible. The introduction of new and smaller cells with higher hemoglobin concentration would have some influence in this same connection. Previous investigators are in agreement that the red cells at birth are larger than those found in the adult, and that they decrease in size during the first week. Börner⁵ reported an average diameter of 8.63 μ at birth but stated that no change was observed during the first 15 days. Mitchell^{38b} later found a decrease in cell volume from 109 to 104 cu. μ in the first 10 days, while Saragea⁴⁴ reported a fall in diameter from 8.6 to 8.3 μ in the first 10 days. It naturally

follows that the volume of packed red cells will vary with the size of the cell measured.

Physiologic destruction of the cells, of course, has no small rôle in the reduction of both the hemoglobin and the volume of packed red cells. Recently Josephs²⁵ has advocated a decrease in cell formation as an additional cause of the fall, which continues over the first 3 months of life. He believed this to be substantiated by the fact that the reticulocytes were diminishing in spite of blood loss. There was no appreciable increase in the total urobilin excreted. Furthermore, administration of iron did not prevent a fall in hemoglobin. Changes in weight have been shown to influence the results, so that rapid increases cause a more rapid fall in blood values, and conversely retarded gain or a loss results in a slower fall. Dehydration, when of a sufficient degree to manifest itself clinically, exerts a marked effect. Another important factor is that of changes in total blood volume, concerning which little work has been done on humans under the age of 1 year. Bawkin² showed that there is a decrease in plasma water during the first 3 to 4 days, but observed the water content to be quite variable in the infant and subject to sudden changes. Later Bawkin and Rivkin³ showed that the volume of blood and plasma in infants is higher in relation to body weight and varies more widely than in adults. They demonstrated that the volume of packed red cells paralleled changes in total blood volume; hence a fall in hemoglobin is due to reduction in circulating cells and not to an increase in plasma volume as some had supposed. We did not carry out blood volume determinations, although we realized the importance of such a study. It is of interest in this connection to observe that Gibson and Evelyn¹⁴ have recently devised an exceptionally accurate photoelectric colorimetric technique for such determinations.

We found a lower average volume of packed red cells for the jaundiced infants, as compared with those not developing icterus, the difference not being appreciable until after the sixth day, when it reaches 4%. We feel, however, that this difference is negligible and will demonstrate our reasons in the forthcoming paper on blood bilirubins. Furthermore, we were unable to demonstrate any relationship between the total change in volume of cells during the period studied and the appearance of clinical jaundice.

Reticulocytes. *Literature.* Krumbhaar^{30a,b} found that reticulocytes reach a maximum of 5% in the first 24 hours of life and are about 3% thereafter until the end of the first week, when they reach normal adult levels of less than 1%. Friedlander and Wiedemer¹³ reported 11% reticulocytes in the first 24 hours, the number steadily and uniformly decreasing to the eighth day, when it reaches adult values. Frank¹² demonstrated that reticulocytes of the newborn are 1 to 9% during the first week. Seyfarth⁴⁶ announced a 5 to

10% range within the first few hours with a fall to 0.3 to 1% in 6 days. Seyfarth and Jurgens⁴⁷ later reported 7% at birth, 2% in 10 days, and 0.7% by 3 weeks. Kato²⁶ gave 1.4 to 1.9% with a maximum of 5.5% and a minimum of 0.1% during the first 36 hours with a fall to 0.5% after 5 days. Goldbloom and Gottlieb¹⁵ found 7% reticulocytes in umbilical blood, 5% on the second day, 3% on the third day, 2% on the fourth and 0.5% on the fifth days. They were practically absent by the sixth day.

Observations. On 41 examinations of the umbilical blood, we found an average of 2.7% (range, 0.2 to 5%). On the second day venous blood, the average of 34 samples was 3.1% (range, 0.3 to 4.5%). On the fourth day, the average of 28 cases was 2.3%, with a distribution of 0.3 to 4.2%. One examination carried out on the fourth day blood of a case of erythroblastosis was 10.6%. On the sixth day 24 samples averaged 1.2% (range, 0.2 to 3%), while on the ninth day the average of 22 cases was 0.34% (range, 0.1 to 0.9%).

Fragility. Literature. A brief review of the outstanding literature pertaining to the fragility of the red blood cells of the newborn gives a picture which varies from decreased to normal to increased resistance of the cells to hemolysis. In adults, hemolysis normally begins in the 0.44 to 0.48% solution and is complete in the 0.34 to 0.4% solution. No one, of course, has published material which has been determined by our method so that we are unable to compare closely our results with similar reports from other investigators. Van-de-Velde⁵² found increased resistance of the erythrocytes in human fetal blood. Hofmeier²² as early as 1882 reported that in adults blood mixed with a 0.25% saline solution showed no red cells remaining, while in newborns the cells were still numerous. He decided after further observation that the resistance of the cells in the first days of life was increased and that by the fourth day had begun to decrease. A greater resistance of the erythrocytes in the newborn than in the adult was reported by Hawksley and Lightwood,²¹ Hornung,²³ Unger,⁵¹ and Viola.⁵³ Simmel and Simmel-Rapp⁴⁹ found an increased resistance in newborn children which simulated that met with in marked and long-continued jaundice of the adult. In the newborn, they found that one-third of the cells remained in the 0.3 solution while one-half to three-quarters remained in the 0.4 solution, and no hemolyzed cells were present in the 0.6 and 0.7 solutions. They observed that the resistance of the cells increased during the first week in children with or without clinical jaundice and that no definite difference between the jaundiced and non-jaundiced could be demonstrated during the first and second weeks. They felt, therefore, that jaundice of the newborn is in no way accompanied by a lowered resistance (increased fragility) of the red blood cells. They observed a fall in resistance beginning the

second week, with normal values obtained by the fourth week. Pollitzer⁴¹ reported that in normal infants as well as in icterus gravis neonatorum, the fragilities were variable.

The same resistance in the newborn as in the adult was found by Knöpfelmacher,²⁸ Mensi,³⁶ and more recently by Cserna and Liebmann,⁸ and Mitchell,³⁸ the latter reporting hemolysis with a range of 0.55 to 0.52% to 0.32 to 0.25%. Slingenberg⁵⁰ found the same resistance but observed an increase in the newborn during the first 4 days which remained higher than in the adult until after the tenth day. In contrast to this, a lessened resistance was found by Cathala and Daunay,⁷ Maliwa,³⁵ and Klima and Rosegger,²⁷ who noted that reticulocytes were especially less resistant. In this connection Goldbloom and Gottlieb¹⁵ reported "a marked increase in the fragility of red corpuscles in cord blood. The same increase in fragility was found in the peripheral blood of infants. The resistance returns to normal or above normal at the end of about 1 week. An increase in the number of immature red cells, reticulated forms and nucleated red cells was found in the cord blood and in the peripheral blood." The disappearance of these immature forms with return of the fragility toward normal was taken by them to mean that the reticulocytes were the cause of the increased fragility noted at birth. Other workers have been unable to demonstrate this, while Sabrazes and Leuret⁴³ consider the reticulocytes to be especially resistant towards hemolysis. Mermod and Dock³⁷ observe that the reticulocytes and young cells resist hypotonic saline unusually well although they are more fragile toward saponin and oxalate or citrate solutions.

Anisohemolysis—the increased span of hemolysis from maximum to minimum solutions—was observed by Jona,²⁴ Whitby and Hynes⁵⁶ and Hallez,²⁰ the latter reporting an average initial hemolysis in the 0.56% solution. Carr⁶ found an average range of 0.45 to 0.28% (maximum, 0.5%; minimum, 0.2%), and also pointed out an increased breadth of hemolysis. Simmel and Simmel-Rapp⁴⁹ made similar observations.

Observations. Using the method of Waugh and Asherman and the Evelyn colorimeter, we carried out fragility tests in conjunction with the previous work. Taking 400 as the average normal adult index of hemolysis and 350 to 450 as the normal range, we calculated the resistance of the red blood cells of the infants. On 52 samples of umbilical blood, we obtained an average index of 400 (range, 280 to 528). On the second day, 45 samples of venous blood gave an average index of 346 (range, 224 to 429). On the fourth day, the average index of 46 cases was 328 (range, 222 to 414). On the sixth day, the average index of 39 infants was 337 (range, 234 to 441). On the ninth day, 37 cases averaged 356 (range, 246 to 471) (see Chart 1).

We felt it best to express our results according to the 20% with the highest indices, the 20% with the lowest indices (greatest resistance) and the 60% intermediate. Chart 1 shows these averages

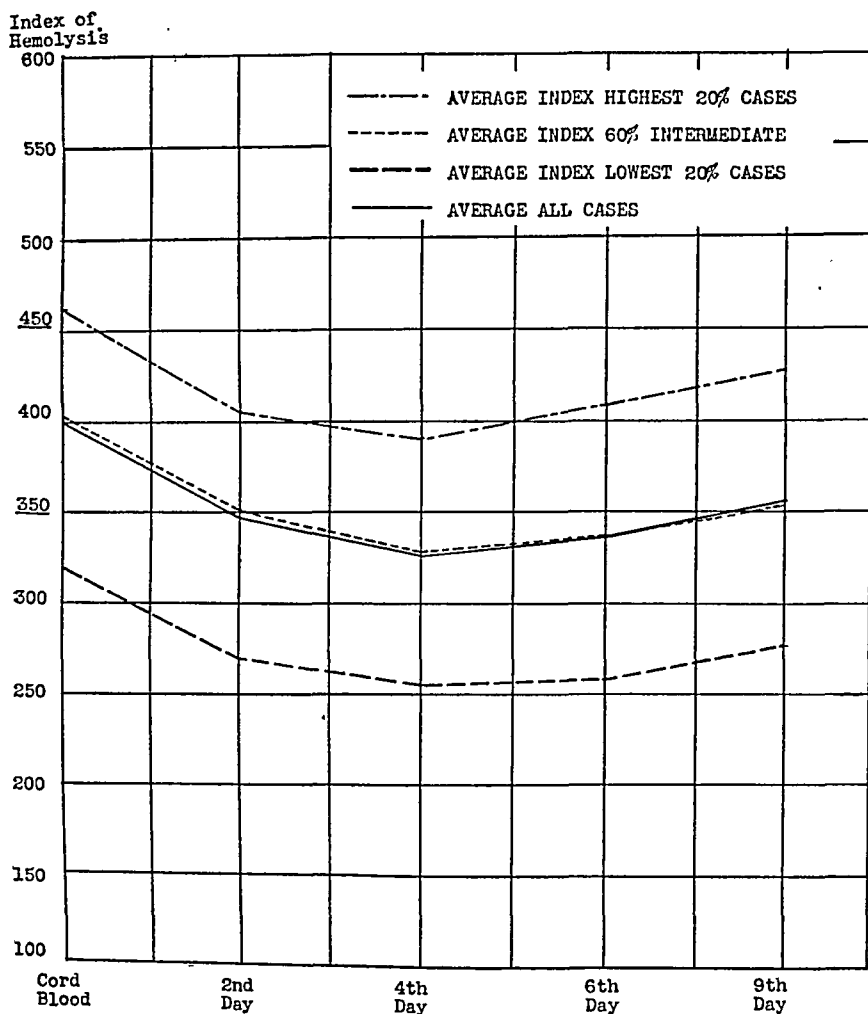


CHART 1.—Averages of indices of hemolysis during the period studied comparing selected group values with averages of all cases.

plotted against the averages for all cases; details are given in Table 4. Here again the 60% intermediate group presents values which are nearly identical with the average for all cases and rules out, we

TABLE 4.—INDICES OF HEMOLYSIS OF ALL CASES, COMPARED WITH THE SELECTED GROUPS.

Time.	No. of cases.	Averages, all cases.	Averages, 20% high.	Averages, 60% mid.	Averages, 20% low.
Cord blood	52	400	466	404	320
2d day	45	346	409	351	269
4th day	46	328	389	330	257
6th day	39	337	415	337	260
9th day	37	356	432	355	280

believe, any marked influence which can be exerted by very high or very low values present in a minority of cases. It is of interest to observe in connection with the determination of the fragilities, that a separate hemoglobin determination is made at the same time the tubes are set up, and in this manner we have a check upon our previous hemoglobin values which were obtained by a slightly different method.

It will be noted that the index of hemolysis for cord blood is at the normal adult figure and there occurs a fall in the index signifying an increased resistance on the second and again on the fourth days, from which point a gradual rise occurs to the ninth day. At no time is there evidence of an increased fragility and the variations met with between high and low figures are the same as have been shown by Waugh and Asherman to exist in the adult. As regards individual cases, it is worthy of note that not a single exception occurred in the character of these changes, the only differences being in the level from which they started.

Because we were aware that hemolysis of the cord blood would take place readily in oxalate solutions,^{15,37} we marked those bloods which were received and slight hemolysis noted in the plasma. Only occasionally was this an appreciable amount, inasmuch as we made our determinations as soon after withdrawal as possible. However, of the 52 samples of cord blood, 18 showed some degree of hemolysis at the time of carrying out the tests. The average index for these cases was 438, as compared with the average of 383 for the 34 non-hemolyzed samples. This would slightly reduce to a more correct figure the index of hemolysis on cord blood, but does not change the general character of the curve, as will be seen by referring to Chart 1.

In dividing the infants into those who did and did not develop jaundice (Table 2) we found that of the 16 cord bloods of infants who later became icteric the average index was 390, as compared with the average of the non-jaundiced cases of 405. On the second day, 15 samples of fontanel blood of infants who became jaundiced averaged 338 while the others averaged 350. On the fourth day, the 14 infants who were jaundiced averaged 335, while the non-jaundiced infants were 328. By the sixth day, the 13 jaundiced infants showed an increase in index to 346, with the non-icteric at 333. On the ninth day, 12 samples from icteric infants averaged 379, while the non-icteric was at 344. In Chart 2 the indices of hemolysis in the two groups of icteric and non-icteric infants are plotted separately against the general averages. It will be noted there is no evidence that icteric infants show an increased fragility. However, the finer detail of change which is brought out by this method does show that in the babies developing jaundice there is an earlier cessation of fall and more rapid return toward normal levels. This may be due in some way to the hyperbilirubinemia. In addi-

tion, 1 case of erythroblastosis on which four determinations were made showed an index of 542 on the umbilical blood, 496 on the second day, 479 on the fourth day, and 454 on the sixth day. A case studied on the third day showed an index of 547 with hemolysis extending throughout all the solutions. Another case studied on the fourth day gave an index of 439. In all these cases there is increased

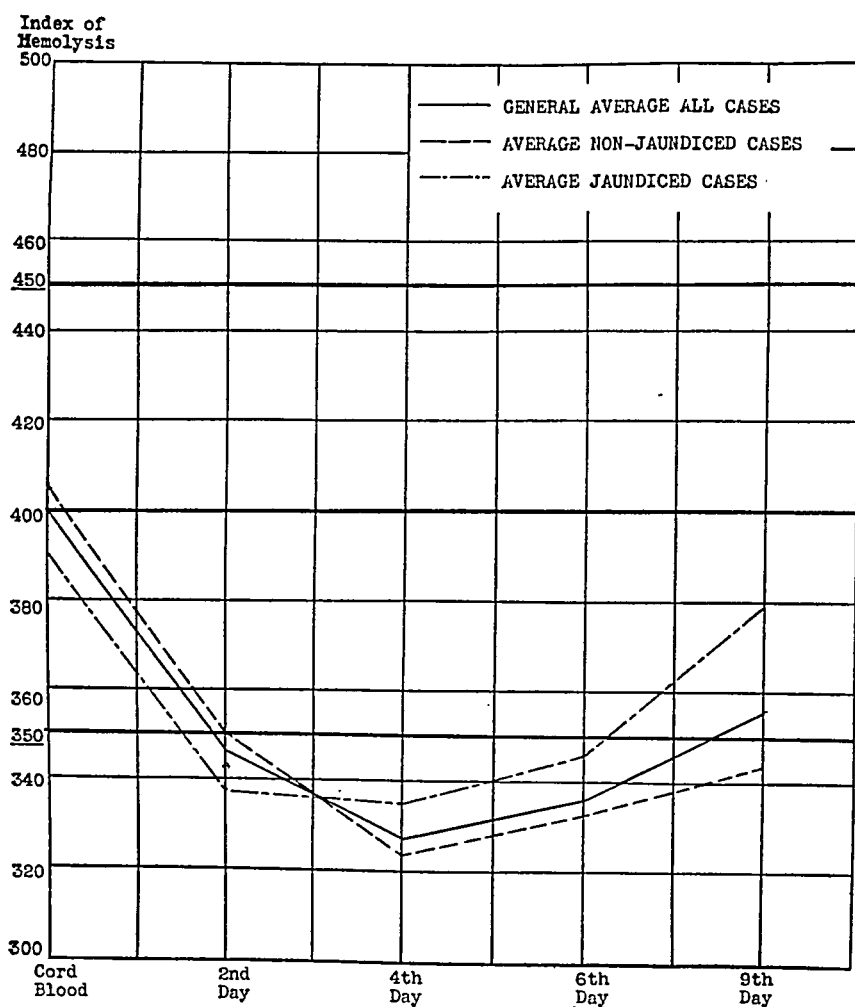


CHART 2.—Comparison of average indices of hemolysis of jaundiced and non-jaundiced infants with general averages during the period studied.

fragility of the red cells which, however, in the first instance shows a tendency to return toward normal.

In order to illustrate the amount of hemolysis in the various dilutions and thus the character of the fragility curve (hemolygram) which is not shown by the hemolytic index, we have compiled Chart 3. In this, the composite curves for each day studied are compared with the average of 50 adults. This clearly demonstrates the anisohemolysis which is present at this age period and which

has been previously reported.^{6,20,24,48,49,56} By this is meant that the erythrocytes show an abnormal spread in the dilutions at which they hemolyze, so that one finds a certain number of cells which are unusually resistant and others which are abnormally fragile. This type of curve is a common finding in many hypochromic anemias

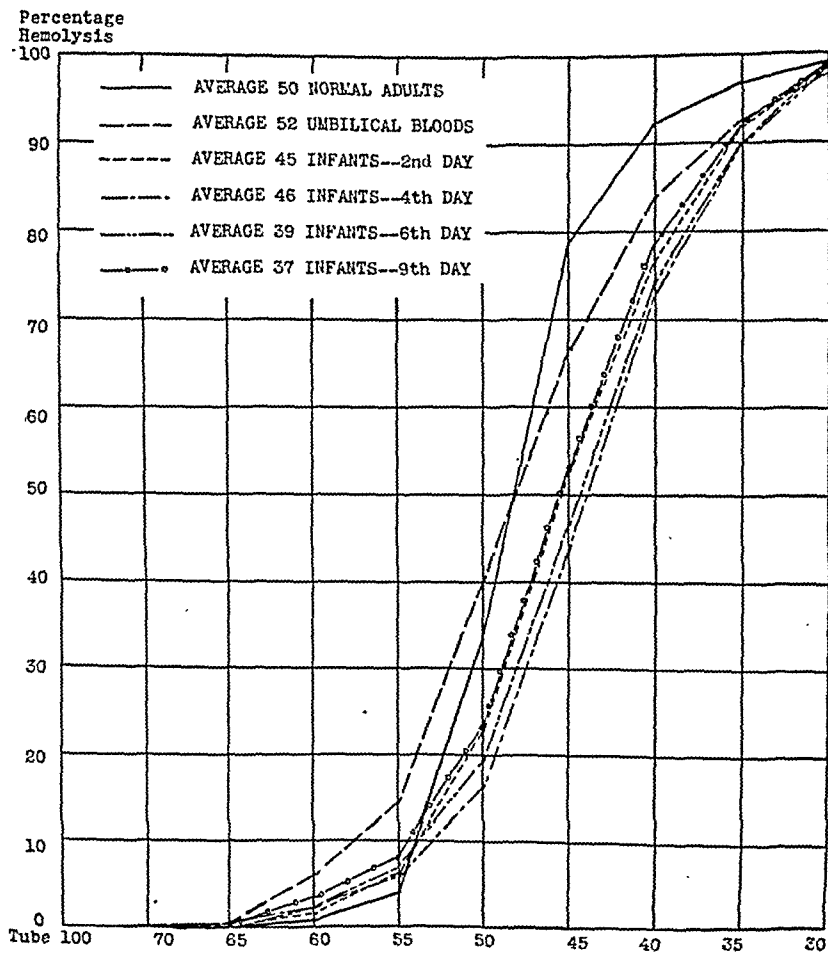


CHART 3.—Comparison of erythrocyte fragility curves (hemolygram) of newborn infant bloods (umbilical, 2nd, 4th, 6th, 9th days) with 50 normal adult males.

of the adult. A similar chart which is not reproduced here showed no difference in the character of the erythrocyte fragility curves in the icteric and non-icteric infants.

In comparing the indices of fragility with the hemoglobin values, no relationship could be demonstrated. At birth, for example, the 20% of umbilical samples with the highest indices (least resistance) had an average hemoglobin of 15.9 gm., while the 20% with lowest indices (greatest resistance) had an average of 15.61 gm. Individually, the widest variations were observed and no prediction as to fragility of the cells could be made from hemoglobin values.

Comment. We have studied some of the blood changes in 60 infants during the first 9 days of life. Our results for hemoglobin and volume of packed red cells are lower for the most part than those generally noted in the literature. We believe that several factors may account for this apparent discrepancy, namely, geographical location, season and climate, and the absence of a standard technique employed by some workers. We have utilized an improved and accurate photoelectric colorimeter hemoglobin technique. Our infants were all full term and within the limits of usual birth weights. The decrease in hemoglobin and volume of packed red cells which we observed during the period of study we believe to be caused primarily by the physiologic destruction of the erythrocytes which takes place during this period. At the same time, we quite appreciate that there are various other factors which are bound to affect the results obtained. These are changes in water content of the cell, changes in blood volume, diminution in size of the cells and, quite possibly, decrease in erythrocyte formation. In this connection, it is of interest to note that we observed an increase in mean corpuscular hemoglobin concentration during the period studied, so that by the ninth day the value was nearly that of adults in this region.

Although our infants who developed clinical icterus showed on the average slightly lower values than did those who failed to develop jaundice, the two groups changed in about the same degree during the 9 days, and we feel that on the whole the differences are negligible. In this connection we believe the distinction between icteric and non-icteric infants on the basis of clinical jaundice to be a deceptive one, but further observations and discussion will be reserved for our next paper which concerns detailed indirect and direct blood bilirubin determinations.

In regard to the fragility of the erythrocytes, we have definitely shown that at birth the index of hemolysis in the newborn is essentially the same as that in the adult, and moreover exhibits a similar individual variation. A fall (increase in resistance) then occurs which continues until the fourth day at which time it has reached a value definitely below that of the normal adult. A gradual rise then occurs which, however, by the ninth day has not as yet attained its original level.

In the studies of the hemolysis curve it is demonstrated that a characteristic type of anisohemolysis is present. This indicates that some unusually resistant and other unusually fragile cells persist throughout the period studied. In the case of infants developing clinical icterus, the changes in resistance of the cells are essentially the same as in the non-icteric, with the exception that there is a slightly earlier cessation of fall and a more rapid return of the resistance toward normal levels. We believe our results on changes in hemolysis during this 9-day period, because of the more

exact methods at our disposal, are particularly conclusive, and exclude any possibility that icterus neonatorum is referable to an increased fragility of the erythrocytes.

Summary. 1. The average total hemoglobin of newborn infants in Montreal at birth is about 15.6 gm. (100%), and falls 0.66 gm. (5% of the original value) within the first 9 days of life.

2. The average volume of packed red cells in newborn infants in this locality is 51.3% (108% of our normal adult's figure), and falls 5.4% (10.5% of the original value) in 9 days.

3. As the decrease in hemoglobin and volume of packed red cells are not identical, it is apparent that the mean corpuscular hemoglobin concentration rises (from 30 to 32%) during the first 9 days, approaching the concentration of adults in this region.

4. The average figures for hemoglobin and volume of packed red cells in infants developing clinical icterus are only slightly lower than in the non-icteric group. No correlation could be demonstrated between the original height or subsequent changes in individual values and the appearance of clinical jaundice.

5. Reticulocyte estimations are similar to those found by other investigators.

6. The fragility of the erythrocytes in newborn infants as determined by the hemolytic index is normal at birth. The index falls, indicating a greater resistance, during the first 4 days, after which it returns toward normal.

7. The erythrocyte fragility curves demonstrate a constant and characteristic degree of anisohemolysis throughout the period studied.

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STUDIES ON CIRCULATION IN PREGNANCY.

IV. VENOUS PRESSURE OBSERVATIONS IN NORMAL PREGNANT WOMEN, IN PREGNANT WOMEN WITH COMPENSATED AND DECOMPENSATED HEART DISEASE AND IN THE PREGNANCY "TOXEMIAS".

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CONFLICTING reports as to the value of the arm venous pressure in normal pregnant women appear in the literature (Table 1). One-half the studies report the arm venous pressure as normal;^{4,7a,13,14,18} the other half report the venous pressure to be high during normal pregnancy.^{2,6,11,19,23} There has been little study of the venous pressure in either compensated or decompensated heart disease during pregnancy. Extremely high venous pressure values have been reported in the pregnancy "toxemias"^{11,19} but certain considerations, to be discussed later, cast doubt on these findings.

The general plan of study outlined previously^{7a} has, where possible, been followed, that is, repeated observations were made on the *same* patient at frequent intervals throughout pregnancy and during the puerperium. In venous pressure studies, as in other investigations of the circulation in pregnancy,^{7,a,b,23,21,22} such a plan of study is most important for the satisfactory understanding of the behavior of hemodynamic changes since variations between different individuals at the same phase of pregnancy may sometimes be greater than changes occurring during the entire pregnancy period in the same individual. This plan of study has been difficult to follow in the toxemic and decompensated cardiac patients except in the few cases in which either toxemia or cardiac failure happened to develop in patients who were already being studied. Hence, in the study of these groups most of the cases were first studied after the complications leading to investigation had developed. Such patients were then usually studied throughout the remainder of pregnancy and in the puerperium.

Methods of Study and Sources of Error. Arm venous pressures were determined according to the direct method of Moritz and von-Tabora.¹⁶ The skin at the site of venipuncture was anesthetized with 2% procaine without adrenalin. The zero point of the manometer was placed, with the aid of a level, at the reported level¹⁶ of the right auricle, *i. e.*, a point 5 cm. dorsal to the junction of the fourth costochondral junction and the sternum, with patient in the supine position. Normal saline was used to fill the apparatus. Actually, the measurements were made in centimeters of normal saline though, as is customary, reported in centimeters of water. All observations were made with the patients fasting and after at least 20 minutes bed rest.

The lowest of at least three determinations which checked each other within 0.5 cm. of water and were satisfactory observations (free flow of saline from manometer, no evidence of extravenous injection, no signs of obstruction, immediate response to obstruction of vein) was taken as the reading for that particular day.

As the literature reveals such conflicting results (Table 1), it is important to consider the *sources of error* in the determination of the venous pressure. Consideration of them includes:

TABLE 1.—ARM VENOUS PRESSURE IN NORMAL PREGNANT WOMEN.
SUMMARY OF LITERATURE.

Observer.	Year.	Method.	No. of cases.	No. of observations.	Results.
Runge ¹⁸	1924	Direct	22	22	Normal
Kaboth ¹¹	1924	?	?	?	High
Carulla ⁶	1926	Indirect	30	30	High
Villaret ²³	1930	Indirect	9	9	High
Krukenberg ¹³	1932	Direct	29	29	Normal
Barath and Weiner ²	1933	?	11	11	High
Strauss ¹⁹	1935	Direct	20	20	High
Cohen and Thomson ^{7a}	1936	Direct	10	41	Normal
Landt and Benjamin ¹⁴	1936	Direct	19	?	Normal
Burwell ⁴	1938	Direct	22	46	Normal

1. The use of an "indirect" method is believed to be a source of error as it has been demonstrated³ that the "indirect" method, when used to determine venous pressure at levels lower than 20 cm. is quite unreliable.

2. It is important that the patient rest quietly for the period of time mentioned above and remain relaxed during the test. Insufficient preliminary rest, and "tenseness" (incomplete general relaxation) lead to erroneous high values which return to lower levels if the examiner awaits relaxation.

3. Internal rotation or abduction of the arm may result in falsely high readings. They also may occur unless there is adequate support to hand and forearm (incomplete local relaxation) on the side in which the needle is inserted. The use of small pillows or a hand-rest as support may overcome this source of error.

4. Readings should not be made until enough time has elapsed for saline in manometer to reach its level. The test is not complete if manometer level is falling, even though slowly. A sound practice is to take as the answer the lowest of three readings, all of which check within 0.5 cm. H_2O .

5. Obesity, in certain individuals, leads to high venous pressure readings.¹⁷

6. During pregnancy the breasts are large and during the last months may cause venous obstruction to arm veins with falsely high venous pressure in the arms, particularly if the patient is in the supine position. In some cases, if the breast or its axillary attachments are shifted slightly by the examiner, there is an immediate fall in venous pressure to a correct lower level, which level may be checked repeatedly. This is believed to be an important source of erroneous high readings in late pregnancy, reflecting temporary venous obstruction and not that of the generalized venous pressure (right auricle).

7. Contractions of the uterus are followed by rise in venous pressure, of sometimes as much as 10 cm. The patient is not conscious of all uterine contractions (Braxton-Hicks) which occur in late pregnancy and may last $\frac{1}{2}$ minute or more. Unless the examiner palpates the abdomen in cases where there is high reading, he cannot be sure that he is not reporting the transient effect of uterine contraction on the venous pressure, rather than the actual venous pressure for that patient. For instance, in Case 223, venous pressure was observed over $\frac{1}{2}$ hour's time to remain constant at 6.7 cm. H_2O . However, on several occasions during examination, it rose abruptly to levels of 12, 14, and 16 cm. and returned, after an interval of about 1 minute, to the level of 6.7 cm. H_2O . Palpation over the uterus revealed definite uterine contraction corresponding to the increased venous pressure. Uterine relaxation corresponded with the return of venous pressure to the lower level, where it remained until another contraction. The patient was completely unaware of these contractions.

The likelihood of error, then, is greatest during the final months of pregnancy, when the breasts are large, the patient has difficulty in maintaining a comfortable position in bed, and the uterus is undergoing Braxton-Hicks contractions. It is of interest to note that it is during this period that high venous pressures have been reported by some observers for normal pregnant women.^{11,19}

Various limits for normal venous pressure have been set by investigators.^{8,10,16,23} For this study, 12 cm. H_2O was regarded arbitrarily as the upper limit of "normal."

Results. The material for this study comprises venous pressure observations on 20 normal pregnant women, 27 compensated cardiatics, 18 decompensated cardiatics and 21 "toxemics."

I. Normal Pregnant Women. On 20 normal pregnant women 94 observations (65 before, 29 after delivery) were made (Table 2). The antepartum values varied between 2.5 and 10 cm. H_2O , average 7.2; the postpartum observations between 3 and 12 cm. H_2O ,

average 7.3 cm. H₂O. All the values were within limits for normal non-pregnant women.

The individual and average venous pressure values were slightly higher in early pregnancy than in mid and late pregnancy and the puerperium (Table 2, Fig. 1). The average venous pressure after

TABLE 2.—THE ARM VENOUS PRESSURE IN 20 NORMAL PREGNANT WOMEN.

Case No., Normal.	Weeks pregnant.								Weeks postpartum.		
	9-12.	13-16.	17-20.	21-24.	25-28.	29-32.	33-36.	37-40.	1-2.	3-6.	7-24.
36	6.0	4.7	4.2	4.0	5.0	7.9	6.4	7.3
38	7.8	7.9	8.0	8.0	8.5	9.5	...	12.0	10.5	9.4
39 . . .	8.8	...	6.1	6.2	...	8.5	10.0	7.5	
40	6.0	6.7	6.1	7.0	6.9	6.8	6.7	
A	10.0	9.0
B	8.5	9.2	7.3		
C . . .	7.8	9.4	8.0	7.0		
D	5.0	6.0	6.3	5.1	7.5	...	6.5
E	10.0	9.1	9.5	...	7.0	7.3	9.0	11.0		
F	6.3	6.2	6.5	7.0	5.5	7.0	...	6.5
G	11.3	9.8	9.1	8.7	9.0		
H	10.0	7.0	2.5	...	4.5		
I	5.1	...	5.5	...	6.0	...	3.0	
J	7.5	7.1		
K	6.0	5.5	...	7.5	9.5	8.0		
L	7.5	8.5		
M	6.5	7.5		7.7
N	6.5	...	5.5	6.9	...	6.5	
O	8.0	5.5		
P	7.5	7.3	6.5	
No. of observations	2	3	6	10	9	10	12	13	15	7	6
Average .	8.3	7.9	8.1	6.9	7.1	7.1	7.1	7.1	7.8	6.7	7.7

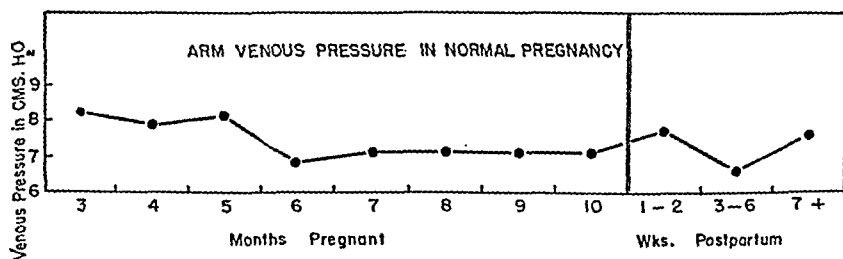


FIG. 1.—The arm venous pressure in normal pregnant women. (Average values based on 94 observations in 20 normal pregnant women.)

the sixth lunar month of pregnancy remained constant at just over 7 cm. H₂O until delivery. There was a slight average increase in the venous pressure in the puerperium as compared with the 21-40th week pregnant values. The late postpartum values are essentially the same as the early pregnancy values and are presumably close to the normal non-pregnant values for the group. In 9 of the 15 cases with observations before or during the second postpartum week the venous pressure was higher early postpartum than at the last antepartum observation, the average of the last pregnant values being 6.6 cm. H₂O, of the postpartum values 8.3 cm. H₂O.

II. A. Compensated Cardiac Patients. On 27 compensated cardiacs 144 observations (104 antepartum, 40 postpartum) were made. Of these patients 21 had rheumatic heart disease (19 Ms, 2 Ms, AR), 5 congenital heart disease (Table 3), 1 had RHD and hypertension. The antepartum values varied between 2.1 and 11.6 cm. H₂O, average 7.2; postpartum the range was between 2.5 and 10 cm. H₂O, average 7.2 cm. H₂O (Table 3).

TABLE 3.—THE ARM VENOUS PRESSURE IN 27 PREGNANT WOMEN WITH COMPENSATED CARDIAC DISEASE.

Case No., Cardiac.	Weeks pregnant.							Weeks postpartum.			Diagnosis.
	9-16.	17-20.	21-24.	25-28.	29-32.	33-36.	37-40.	1-2.	3-6.	7-24.	
31	9.1	7.1	...	8.1	9.5	Rheum. ht. dis., mitral stenosis
37	7.4	6.3	...	8.1	Rheum. ht. dis., mitral stenosis
39	5.8	...	8.9	...	Rheum. ht. dis., mitral stenosis
41	2.7	5.3	5.0	4.2	3.3	3.3	2.7	...	5.1	Rheum. ht. dis., mitral stenosis, aortic regurg.
46	10.5	8.0	...	4.1	Rheum. ht. dis., mitral stenosis
47	8.6	9.8	9.6	6.8	7.3	8.9	...	6.9	Rheum. ht. dis., mitral stenosis
48	9.3	8.5	7.0	6.1	...	Rheum. ht. dis., mitral stenosis
53	7.1	5.4	6.5	6.5	5.3	7.5	...	6.5	5.5	Cong. ht. dis., lesion?
55	10.0	9.5	9.9	10.0	11.8	10.0	9.0	Rheum. ht. dis., hypertensive ht. dis.
57	8.5	7.8	9.5	6.0	7.6	6.0	...	6.8	...	Rheum. ht. dis., mitral stenosis
64	7.3	8.8	11.4	11.5	10.5	9.8	8.0	9.0	...	Rheum. ht. dis., mitral stenosis
67	7.7	9.0	9.9	9.5	9.8	9.0	9.0	Rheum. ht. dis., mitral stenosis
70	6.3	8.1	8.1	8.0	8.5	8.5	8.5	Rheum. ht. dis., mitral stenosis
73	8.5	9.7	6.8	5.0	...	7.5	6.3	Cong. ht. dis., interventricular septal defect
74	4.5	4.7	3.0	3.5	2.2	2.1	...	5.0	7.5	Rheum. ht. dis., mitral stenosis
76	8.5	5.5	6.5	...	4.8	8.0	...	9.5	9.7	Cong. ht. dis., coarctation of aorta
77	3.5	4.2	3.1	Cong. ht. dis., interventricular septal defect
78	7.0	6.2	3.5	3.5	...	5.5	...	2.5	...	Rheum. ht. dis., mitral stenosis
88	10.0	9.5	9.5	...	9.0	7.5	7.0	8.8	Cong. ht. dis., patent ductus Botalli
87	8.5	7.5	9.5	...	8.0	9.0	10.3	...	Rheum. ht. dis., mitral stenosis, aortic regurg.
83	9.0	8.0	...	6.0	7.5	...	Rheum. ht. dis., mitral stenosis
84	5.5	6.0	...	5.8	5.5	8.0	Rheum. ht. dis., mitral stenosis
86	8.5	9.0	9.0	9.7	10.0	...	8.0	...	Rheum. ht. dis., mitral stenosis
85	8.5	...	9.1	6.5	Rheum. ht. dis., mitral stenosis
82	9.5	...	10.0	...	Rheum. ht. dis., mitral stenosis
90	8.5	...	6.8	...	Rheum. ht. dis., mitral stenosis
92	5.5	7.4	...	8.5	8.9	Rheum. ht. dis., mitral stenosis
No. of observations	3	12	16	15	15	20	23	11	18	11	
Average	9.5	7.2	7.6	7.6	8.0	6.9	6.5	6.8	7.2	7.5	

The individual observations and the average values showed changes throughout pregnancy and the puerperium similar to those observed in the normal pregnant group. There was a distinct tendency for the average venous pressure to diminish in the latter months of pregnancy and to return to the early pregnancy level in the puerperium (Table 3).

In venous pressure, as in blood volume²² and circulation time,^{7a} it is of interest to note that the compensated cardiac pregnant woman behaves exactly as the normal pregnant woman.

The type of heart lesion appeared to have no effect on venous pressure.

B. Decompensated Cardiacs. Sixty-four observations (47 antepartum, 17 postpartum) were made on 18 patients who developed heart failure during pregnancy. In all but 1 (Case 52, who developed paroxysmal nocturnal dyspnea) cardiac failure was of the congestive type. Persistent râles at the lung bases was the sole criterion

for heart failure in these patients.^{5,15} In only 2 was there evidence of severe peripheral edema.

In the entire group there were 5 cases with pre-failure observations; in 12 post-failure observations were made; in 4 cases there were both pre- and post-failure observations and in 3 there was more than 1 observation when the patient showed evidence of heart failure. There were 24 antepartum observations made in the absence of congestive failure in patients who were to develop or had developed congestive failure. These values ranged from 3.9 to 10.5 cm. H₂O, with an average of 6.8 cm. H₂O. There were 23 observations made during failure, which ranged between 3.8 and 12.5 cm. H₂O with an average of 7.2 cm. H₂O (Table 4).

One patient developed heart failure in the 3d, 1 in the 4th, none in the 5th, 2 in the 6th, 6 in the 7th, 3 in the 8th, 4 in the 9th, and 1 in the 10th lunar month; none postpartum (Table 4). Seventeen postpartum observations on 11 patients who had showed unmistakable signs of congestive heart failure during pregnancy varied between 3.4 and 9.8 cm. H₂O, with an average of 6.1 cm. H₂O.

TABLE 4.—THE ARM VENOUS PRESSURE IN 18 PREGNANT WOMEN WITH CARDIAC DISEASE WHO DEVELOPED HEART FAILURE DURING PREGNANCY.

Case No., Cardiac.	Weeks antepartum.								Weeks postpartum.			Diagnosis and remarks. §
	9-12.	13-16.	17-20.	21-24.	25-28.	29-32.	33-36.	37-40.	1-2.	3-6.	7-24.	
43	7.7*	6.7	3.4	5.5	...	R.H.D., mitr. sten., aor. regurg., Ces. sect. at 39 wks.
45	5.2	3.9	5.7*	4.5	4.0	4.3	R.H.D., mitr. sten., Ces. sect. at 39 wks.
50	7.7	7.1	8.7	9.9*	6.7*	7.3	7.5	6.5	5.1	...	R.H.D., mitr. sten., preg. terminated at 35 wks.
51	8.0	4.8	7.0*	7.0*	6.1	8.5	...	R.H.D., mitr. sten., Ces. sect. at term
52	6.4	5.7	6.9	7.0	7.3	4.9† 6.7	R.H.D., mitr. sten., aor. regurg., Ces. sect. at term. Pt. died 3 wks. postpartum of ac. bact. endocarditis
54	3.8*	R.H.D., mitr. sten.
58 . . .	5.7*	4.9	4.6	...	R.H.D., mitr. sten., preg. terminated at 26 wks.
61	3.9*	R.H.D., mitr. sten., Ces. sect. at term
63	5.5*	R.H.D., mitr. sten., aor. regurg., Ces. sect. at 37 wks.
65 . . .	7.0	6.8*	5.7	...	6.5	R.H.D., mitr. sten., aor. regurg., preg. terminated at 16 wks.
71	12.5†	Hypertens. ht. dis., "toxemia," Ces. sect. at 34 wks.
75	8.5*	8.3	6.5	...	7.0	R.H.D., mitr. sten., aor. regurg.
76	8.5*	7.5	...	R.H.D., mitr. sten.
78	9.0*	10.5	9.8	Cong. ht. dis., lesion?
94	7.5*	7.0	5.5	...	6.3	...	R. and cong. ht. dis., mitr. sten., patent duct. Bot.
96	8.0*	6.5	R.H.D., mitr. sten., pat. died undeliv'd at 30 wks. of subac. bact. endocard.
98	5.0†	5.0	Hypertens. ht. dis.
99	11.0*	R.H.D., mitr. sten., pat. died undeliv'd at 31 wks. of ac. resp. infection and meningitis

R.H.D. = Rheumatic heart disease.

* Congestive heart failure.

† Paroxysmal nocturnal dyspnea (cardiac asthma).

‡ Congestive heart failure, "toxemia."

§ Unless otherwise noted patients delivered through the pelvis at term.

The type of cardiac lesion appeared to have no effect on the venous pressure. Although the venous pressure in these patients was within normal limits, except in 1 instance (Case 66, where there was massive edema), it is of interest to note that in 2 (Cases 45 and 50) where pre- and post-failure observations were made, the venous pressure was highest when there were signs of heart failure, although these values were not above the "normal" range (Table 4). In 1 (Case 51) with pre- and post-failure observations, clinical congestive failure was not accompanied by the highest observed venous pressure.

As compared with both normal pregnant women and compensated cardiacs, either individually or as groups, the value of the venous pressure even during congestive heart failure showed no significant difference. However, a non-clinic neglected case (No. 71) in whom congestive heart failure was advanced and was associated with considerable peripheral edema, showed the only venous pressure above normal encountered in the normal, compensated cardiac, or decompensated cardiac groups. Patients with heart disease who developed "toxemia" are discussed under "toxemia of pregnancy."

It is emphasized that all the cardiacs in this group were under careful supervision with restricted activity and weekly examination for signs of congestive heart failure or pulmonary congestion. The patients were hospitalized immediately when the earliest sign of heart failure, *i. e.*, constant râles at lung bases, appeared. These patients usually lacked symptoms of heart failure except fatigue and their dyspnea and edema were usually within the limits of normal pregnancy. Complete bed rest, diet, fluid restriction and digitalis constituted the hospital régime for these patients and venous pressure readings were usually made after 12 hours to several days of bed rest. Under these circumstances, as is known,¹ elevated venous pressure is not constant in mild congestive failure.

III. "*Toxemias of Pregnancy.*" Seventy-four observations (50 before, 24 after delivery) were made on 21 pregnant women diagnosed "toxemia of pregnancy." The patients were grouped according to the classification of Reid and associates.¹² There were 8 patients (Table 5A) in Group A, *i. e.*, with evidence suggesting hypertensive disease independent of pregnancy. There were 13 (Tables 5B and 5C) patients in Group B, *i. e.*, with no evidence of hypertensive disease until the latter months of pregnancy; of these, 4 (Table 5C) showed eclampsia, the other 9 (Table 5B), preëclampsia. In the latter group there were, by chance, 3 patients who developed toxemia during the course of circulatory studies. The venous pressure values for the "toxemias" of pregnancy did not exceed 14 cm. H₂O, a value given¹⁰ as the outside limit of normal. However, it can be noted on further inspection that more values fell in the upper normal range than in the non-toxic pregnant group.

In Table 5A are presented data of the essential hypertension group. In addition to venous pressure data, there are charted obesity, maximum albuminuria and maximum blood pressure. The term "obesity" is reserved for patients who not only exceeded the average weight for their height, but in addition appeared "obese" to the casual glance. Patients over 200 pounds are indicated by ++. Albuminuria is recorded in terminology of the Massachusetts General Hospital.²⁴ Some of these patients had complicating hypertensive heart disease and others did not. The venous pressure level of patients in this group is slightly higher than that of the normal pregnant women. It is noted further, however, that the higher venous pressure values were all present in patients with obesity. In the 2 patients without obesity, the values were at the lower limits of normal. Since obesity¹⁷ has been described as a cause for elevation of venous pressure, this association may be more than coincidental.

TABLE 5A.—THE ARM VENOUS PRESSURE IN PATIENTS WITH TOXEMIA OF PREGNANCY.

(Essential Hypertension Group—8 cases, 31 observations.)

Case No.	Weeks pregnant.						Weeks postpartum.						Diagnosis and remarks.
	17-20.	12-24.	25-28.	29-32.	33-36.	37-40.	1-2.	3-6.	7-24.	Obes.	Max. alb.	Max. B.P.	
201.	5.0	6.0	...	0	T	220/140	Ess. hypertension, Cess. in 35th wk.
202.	10.5	10.5	8.5	...	8.0	...	++	T	230/140	Ess. hypertension, hypertens. ht. dis., amebic dys.
203.	8.0	...	10.0	8.0	8.5	...	9.0	+	VST	148/108	Ess. hypertension
204.	10.5	...	8.0	8.0	8.0	11.3	8.5	...	8.3	+	VST	170/104	Ess. hypertension
205.	9.5	...	8.0	9.0	9.0	7.8	7.7	+	0	168/110	Ess. hypertension
206.	7.5	8.5	+	T	170/100	Ess. hypertension
207.	...	7.5	7.5	8.0	+	T	180/100	Ess. hypertension
208.	3.1	...	5.0	0	T	180/110	Ess. hypertension, hypertens. ht. dis., card. decomp.

In the 9 preëclamptic patients described in Table 5B, it can be seen that most of the values fell within the upper normal range. A striking phenomenon in this group is that the venous pressure falls immediately postpartum. This contrasts with normal pregnancy⁴ where a slight rise in venous pressure follows delivery (Table 2). In Case 212, venous pressure was 13 cm. H₂O. This reading was made while the patient was in severe congestive heart failure. There were moist râles throughout both lungs, there was massive edema and there had been a severe attack of cardiac asthma a few hours preceding the test.

Case Abstracts. Case 213 merits special attention as this was the only normal pregnant woman being studied who developed "toxemia." Her initial venous pressure was 2.5 cm. H₂O, the second venous pressure in the seventh month of pregnancy was 7.3 cm. H₂O. At this point blood pressure was normal, there was no edema, and no albuminuria. In the ninth month,

TABLE 5B.—THE ARM VENOUS PRESSURE IN PATIENTS WITH TOXEMIA OF PREGNANCY.
(Preëclamptic Group—9 cases, 34 observations.)

Case No.	Weeks pregnant.					37-40.	Weeks postpartum.					Diagnosis and remarks.	
	10-16.	17-20.	21-24.	25-28.	29-32.		33-36.	1-2.	3-6.	7-24.	Obes.		Max. alb.
210				10.0 174/98 L.T. Ed.+			5.5 146/100 0 No Ed.	8.0 128/90 0 No Ed.		0	L.T.	174/98	Pre-eclampsia, severe. Del. by Braxton-Hicks version at 27 weeks
211					9.5 160/108 T. Ed.		8.3 130/90	8.5 130/90		++	T.	160/110	Pre-eclampsia, severe
212					13.0 148/110 L.T. Ed.		8.5 124/80 0 No Ed.	11.0 104/70 0 No Ed.		++	L.T.	166/110	Pre-eclampsia, severe; rales in chest; erythrobl. fetalis
213				7.3 120/70 0 No Ed.		7.0 170/100 L.T. Ed.+	3.5 116/78 0 No Ed.	4.3 110/72 0 No Ed.	0	0	L.T.	170/100	Pre-eclampsia, severe; Ces. sect. at 36th week
214				11.0 156/102 L.T. Ed.+			9.0 120/80 S.P.T.			0	L.T.	166/110	Pre-eclampsia, severe
215						8.2 166/110 L.T. Ed.+				++	L.T.	166/110	Pre-eclampsia, severe; Ces. sect. at term; died of sepsis, 2 days later

Rheumatic heart disease complicated by pre-eclamptic toxemia.

216		8.5 106/70 0 No Ed.	9.0 106/70 0 No Ed.	9.0 126/80 0 No Ed.	9.7 110/70 0	10.0 160/90 T. Ed. +		8.0 136/90 V.S.T.	0	L.T.	180/90	Pre-eclampsia, severe; rheu. ht. dis.; mitr. sten.
217	9.0 100/40 No Ed.	10.0 104/60 No Ed.	11.0 100/50 No Ed.		8.5 110/70 No Ed.	14.0 160/90 L.T. Ed.		5.9	+	L.T.	174/116	Pre-eclampsia, severe; rheu. ht. dis.; mitr. sten.; cong. ht. fail.
218				13.0 152/90 L.T. Ed. + +			8.0 136/90 V.S.T.	8.3 94/60 0	+	L.T.	152/102	Pre-eclampsia, severe; premature separation of the placenta; rheu. ht. dis.; mitr. sten.

however, venous pressure was 7 cm. H₂O, blood pressure was 170/100 mm. of Hg, and massive edema and albuminuria had developed. In the tenth month, venous pressure was 8 cm. H₂O, there were edema, albuminuria, and hypertension and it was not until the postpartum period, when blood pressure was normal and edema was absent, that the venous pressure again returned to the low level observed before development of toxemia. The slight rise in venous pressure, in this case, preceded the development of clinical toxemia.

Cases 216 and 217 are cases of mitral stenosis who developed severe preëclamptic toxemia while being studied. In the first case there is no significant rise in venous pressure after the development of hypertension. In the second case, the development of hypertension and albuminuria in the tenth month of pregnancy was associated with edema, congestive heart failure and rise of venous pressure to 14 cm. H₂O. This is the highest value obtained in the entire study and is an example of congestive heart failure and preëclamptic toxemia developing in the tenth month of pregnancy in an obese woman. Following delivery, the venous pressure dropped to 5.9 cm. H₂O and the signs of congestive heart failure disappeared. Case 218, with a venous pressure of 13 cm. H₂O in the eighth month of pregnancy is another example of the combination of preëclamptic toxemia and mitral stenosis.

The eclamptic group, Table 5C, includes only 5 cases.

Case 221 was a 37-year-old woman who began having convulsions in the thirty-fourth week of her pregnancy. On the day of onset of convulsions and following 5 convulsions venous pressure measured 9.5 cm. H₂O, arterial blood pressure was 208/124 mm. of Hg, there was a large trace of albumin in the urine and marked edema was present. The patient was under influence of sedatives (sodium luminal, magnesium sulphate) at time studies were made. Two days later the patient was delivered and on the fourth day postpartum the venous pressure was 8 cm. H₂O and arterial blood pressure was 174/86 mm. of Hg. On the thirteenth day postpartum venous pressure was 7.5 cm. H₂O and arterial blood pressure was 142/82 mm. of Hg. This patient subsequently developed acute bacterial endocarditis and succumbed to it.

Case 222 had 1 convulsion. On the day preceding it the venous pressure was 6.3 cm. H₂O and the arterial blood pressure 210/120 mm. of Hg, there were râles in the chest and the observed vital capacity was 1700 cc. On the following day, 3 hours after her only convulsion, the venous pressure was 13 cm. of H₂O and arterial blood pressure 200/120 mm. of Hg. At time of study, the patient was quiet. She was delivered 31 hours later by the aid of a Voorhee's bag. Six weeks postpartum her venous pressure was 9.5 cm. H₂O, arterial blood pressure 152/98 mm. of Hg, the râles had disappeared from the chest and the observed vital capacity was 2930 cc.

Case 223 was a 23-year-old woman who was hospitalized because of the rapid development of edema and hypertension. She had gained 41 pounds in her pregnancy and 12 pounds in the eighteenth week, during which she was hospitalized. Studies at this time showed venous pressure of 6.7 cm. H₂O, arterial blood pressure of 167/94 mm. of Hg, marked generalized edema and a slight trace of albumin. The patient was delivered 3 days later and soon after delivery had one convulsion. Thirteen days postpartum the venous pressure was 7.1 cm. H₂O. All edema had disappeared and there was but a slightest possible trace of albumin in the urine. Case 224 was observed to have a venous pressure of 8 cm. H₂O 40 hours after the first convulsion. It can be seen from these data that slight, if any, elevation of the venous pressure occurs in coincidence with eclampsia. No measurements were made in any case during a convulsion. In Case 225, venous

TABLE 5C.—ECLAMPTIC GROUP—5 CASES, 10 OBSERVATIONS.

Case No.	Weeks pregnant.						Days postpartum.						Diagnosis and remarks.
	29.	29.	33.	34.	38.	40.	4.	13.	42.	Obes.	Max. alb.	Max. B.P.	
221				9.5 208/124 L.T. Ed.+			8.0 174/86 V.S.T.	7.5 142/82 S.P.T.		+	L.T.	230/128	9 convul. on same day as initial VP determination; died of bact. endoc.; cbr. accident
222	6.3 210/120 L.T. Ed.+	13.0 200/120 L.T. Ed.+							9.5 152/98 0 No Ed.	++	L.T.	230/160	1 convul.; râles at both lung bases
223					6.7 160/94 S.T. Ed.+			7.1 138/90 S.P.T. No Ed.		+	L.T.	170/110	2 convul.; VP observation 3 days before onset of convulsions
224						8.0 174/86 L.T. No Ed.				+	L.T.	210/110	5 convul.; died in "shock" 2 days postpartum; first convul. preceded by VP determination by 40 hrs.
225			5.5 174/104 L.T. Ed.+							0	L.T.	174/104	3 convul. 2 days before VP observation

Venous pressure is expressed in cm. H₂O. Presence of obesity indicated by +, marked obesity (200 or more lbs.) by ++, and absence of obesity by 0 in vertical column labeled "Obes." Maximum albuminuria during pregnancy is symbolized as follows: S.P.T. = slightest possible trace; V.S.T. = very small trace; S.T. = slight trace; L.T. = large trace²⁴. Maximum arterial blood pressure during pregnancy expressed in mm. Hg. In Tables 5B and 5C, simultaneous data on venous pressure, arterial blood pressure, albuminuria and edema are given. Edema is denoted by Ed., marked edema by Ed.+, and no edema by No Ed.

pressure observation was made 3 days after the onset of convulsions. The patient was still undelivered. Albumin, hypertension, but a normal venous pressure were present.

Discussion. 1. *Control Values.* In addition to those studies made within 2 weeks after delivery, 13 observations were made on the normal group from 3 weeks to 6 months after delivery. These values, which were assumed to be the normal non-pregnant values for these women, ranged from 3 to 10.5 with a mean of 7.1 cm. H₂O and are similar to other normal figures in the literature.^{10,16}

2. *Normal Pregnant Women.* The results of this study indicate that the venous pressure in normal pregnant women remains within the range of values for normal non-pregnant individuals. The discrepancy between these findings and those of observers reporting an elevated venous pressure^{2,6,11,19,23} in normal pregnancy requires some explanation. The use of an indirect method by 2 of the observers^{6,23} may have been a factor in their studies since it has been shown³ that such a method is unreliable in determining venous pressure at levels under 20 cm. The other sources of error outlined may also have been contributory.

In 2 studies^{2,11} the choice of method is not outlined. The paucity of observations makes analysis of the data impossible. In the other study¹⁹ giving results at variance with those reported here (although the direct method was used), individual observations only were made, and then late in pregnancy when errors are so frequent. For these reasons the results cannot be accepted without reservation.

In contrast are the 5 other corroborative studies,^{4,7a,13,14,18} where the venous pressure is described as being within normal limits. In each, the method of Moritz and von Tabora¹⁶ or some modification^{10,13} was used. In Studies 7a and 13 the observers report careful checking of individual observations.

Our study is lacking in observations on patients before pregnancy and also in the early months of pregnancy. More data should be obtained on the venous pressure in early pregnancy because, as suggested in another study,¹⁴ and as indicated in the data of Tables 2 and 3, there seems to be a higher venous pressure in the early months of pregnancy than in the latter months. There is no conclusive explanation for this. A possible explanation, which however is at best speculative, concerns the increase in blood volume²² occurring in early pregnancy and the increase in the superficial venous channels, as shown by the infra-red studies on the veins of pregnant women.⁹ Is it not possible if the increase in blood volume early in pregnancy occurs rapidly that there may be a time lag before adequate venous channels develop, with a consequent early rise in venous pressure? The slight increase in venous pressure postpartum may be associated with lactation and in the infra-red vein studies made at this clinic⁹ it was demonstrated that, whereas the abdominal veins receded postpartum, the veins over

the breasts and thorax became, if anything, more prominent. Venous pressure observations in the legs^{4,18} have been reported as elevated in patients whose arm venous pressures were within normal limits. Our observations of femoral venous pressure, though scant, are corroborative.

3. *Pregnant Women with Heart Disease—Compensated and Decompensated.* Values for arm venous pressure in pregnant women with compensated heart disease were almost identical with those of normal pregnant women (Tables 2 and 3). This coincides with the usual finding that venous pressure is normal in compensated heart disease.¹

In the group of cardiac patients with congestive failure the values remain within normal limits. In most cases persistent râles in the chest constituted the chief sign of failure. Marked peripheral edema was usually lacking. Venous pressure measurements, as well as clinical observations, then, support the general idea that so-called left-sided heart failure is the type to be expected in pregnancy. Despite occasional small increases in venous pressure (see Case 50) accompanying heart failure, the venous pressure is, unlike the vital capacity,^{7b} of no value in the prediction or diagnosis of early heart failure in pregnancy.

In 3 cases of rheumatic heart disease, complicated by toxemia of pregnancy the highest venous pressure readings were recorded. Peripheral edema and albuminuria were present in all. Case 217, with obvious heart failure, showed a venous pressure of 14 cm. H₂O, the highest in the study, with a return to 5.9 cm. H₂O postpartum. This small amount of evidence adds to the clinical impression that toxemia of pregnancy may be an especially serious complication in the presence of organic heart disease.

4. *Toxemias of Pregnancy.* The number of observations in this group and their lack of complete consistence makes any broad conclusion from them unwarranted. However, certain points seem clear. These values do not corroborate the extremely high ones found by one observer¹⁹ who found one-half of 20 values ranging from 13 to 21 cm. H₂O. Since this observer also found similar values in normal pregnant women and reports that he found in toxemics "a value not significantly different from normal pregnant women," it is difficult to compare his results with those presented in this study. Extremely high venous pressure readings were reported by another investigator¹¹ in 3 cases of eclampsia. This observer also reported high values in normal pregnant women. One of the cases reported by this observer showed an elevation of venous pressure above 50 cm., with marked fluctuations, with the values rising and falling rapidly. In this instance Braxton-Hicks contractions of the uterus were not ruled out as a possible explanation of the changes.

From this study it appears that, accompanying toxemia of preg-

nancy, there is apt to be a slight rise in venous pressure from the pre-toxemic level, but that the rise is not an extreme one. The level of the venous pressure in no way correlated with the severity of the illness, the amount of edema or the arterial blood pressure. There is no crucial data in this study to indicate whether the slight rise in venous pressure contributes to form the edema, results from the edema, or is actually related to the edema. The drop in venous pressure immediately postpartum is an interesting difference from the usual trend in pregnancy.

There is no striking variation of the venous pressure in eclampsia in relation to the onset of convulsions. The highest values in venous pressure observed in this study were in patients with toxemia of pregnancy and previous heart disease.

Conclusions. 1. The arm venous pressure, as measured by the method of Moritz and von Tabora, is within "normal limits" during normal pregnancy.

2. This study corroborates the studies of others who find the venous pressure in normal pregnancy within normal limits and points out possible sources of error in those studies which report increase of venous pressure in normal pregnancy.

3. The venous pressure of normal pregnant women tends to diminish from early pregnancy to the sixth month, remains fairly constant throughout the remainder of pregnancy, rises slightly in the early puerperium and returns to the early pregnancy level later postpartum.

4. This same trend is present in pregnant women with compensated heart disease.

5. The measurement of venous pressure cannot be used to predict or diagnose early congestive heart failure in pregnant cardiac women.

6. There is probably a slight increase in venous pressure accompanying "toxemia" of pregnancy.

7. The venous pressure decreases immediately postpartum in patients with "toxemia" of pregnancy, in contrast to normal pregnant women in whom it usually rises.

8. This study does not corroborate the finding of extremely high venous pressures in "toxemias" of pregnancy.

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COR PULMONALE DUE TO OBSTRUCTION OF THE PULMONARY ARTERY BY SYPHILITIC AORTIC ANEURYSMS.

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It is well known that syphilitic aneurysms of the aorta which do not involve the aortic valve area may be present without evidence of heart failure, whereas aneurysms involving the aortic root with dilatation of the aortic valve ring frequently result in death from myocardial insufficiency. Such cases, presenting the clinical picture of aortic insufficiency, rarely offer any difficulty in diagnosis.

This communication points out a much more unusual way in which an aortic aneurysm may cause myocardial insufficiency, *i. e.*, by chronic compression of the pulmonary artery. Pressure upon the pulmonary artery is one of the less common complications of aneurysms of the aorta. The usual result in such cases is rupture of the aneurysm into the pulmonary artery. The dramatic and characteristic course of events in this phenomenon has been adequately described by Scott.⁹ More rarely, however, the aortic aneurysm does not rupture but causes a chronic stenosis of the pulmonary artery. This burdens the right side of the heart, resulting in hypertrophy and dilatation of the right ventricle—the so-called *cor pulmonale*.

This combination of aneurysm and heart disease is very unusual and difficult to diagnose. The literature contains only scattered reports of its occurrence, notably those of Pollack,⁵ Rindfleisch and Obernier,⁶ Gairdner,⁴ Arnold,¹ Bufalini,² Schlesinger,⁸ Rohr and Ryffel,⁷ Costa,³ and Tibirica and Bittencourt,¹⁰ most of which have

been particularly concerned with the anatomic findings. The following 3 cases are reported in order to direct attention to the clinical significance of this condition, *i. e.*, that compression of the pulmonary artery may be the cause of heart failure in those cases of aneurysm of the aorta in which involvement of the aortic orifice is not demonstrable.

Case Reports. CASE 1.—H. H., a 57-year-old white carpenter, entered Cleveland City Hospital, January 9, 1938. His chief complaint was swelling of the legs of 4 months' duration. The patient had been in good health until 1935, when he began to have periodic attacks of pain in the chest. At that time fluoroscopic and film studies of the chest showed a large aneurysm of the first portion of the arch of the aorta. The transverse diameter of the aortic shadow measured 14 cm. in width (Fig. 1).

After antiluetic treatment the patient was in fairly good health until about September, 1937, when he developed shortness of breath, cough, swelling of the feet, weakness, and swelling of the abdomen. These symptoms became progressively more severe. Shortly before admission, he had had an attack of severe precordial pain, and subsequently had been very short of breath and acutely ill. He had had a penile chancre at the age of 18.

Examination showed the patient to be normally developed and fairly well nourished, but he was cyanotic, orthopneic, and acutely ill. The neck veins were markedly distended. There were râles at the bases; the liver was enlarged and tender; the abdomen contained fluid; and the trunk, genitalia and legs showed moderate pitting edema. The heart was enlarged and the cardiac mechanism was normal except for tachycardia. There was a systolic murmur of moderate intensity audible over the entire precordium. A tracheal tug was demonstrable, and there was a pulsating mass in the left upper chest. The blood pressure measured in millimeters of mercury was 130 systolic and 60 diastolic.

The blood Kline test for syphilis was 4+; the blood Wassermann test was negative. The urine contained albumin Grade 2.

The patient did not improve despite treatment and died on the third hospital day, January 12, 1938, of congestive heart failure. The clinical diagnosis was: 1, syphilitic aneurysm of the ascending aorta; 2, myocardial insufficiency, probably due to coronary artery sclerosis; 3, possible coronary thrombosis.

AUTOPSY. External examination was negative except for pitting edema of the legs and genitalia. The peritoneal cavity contained 300 cc., the right pleural space, 700 cc., the left pleural space, 900 cc., and the pericardial space, 200 cc. of serous fluid.

The heart weighed 425 gm. The right atrium and the right ventricle were dilated and hypertrophied, the ventricular wall measuring 0.7 cm. in thickness. In contrast the left atrium and ventricle were not significantly enlarged, the ventricular wall measuring 1.5 cm. in thickness. There was no narrowing of the coronary ostia and the arteries did not show noteworthy arteriosclerosis. There were no areas of infarction. The heart valves were normal.

The aorta showed a typical syphilitic aortitis with a large aneurysm involving the ascending limb and the adjacent portion of the arch. This aneurysm bulged forward and to the left in such a way as to compress the pulmonary artery. In fact, upon opening the pulmonary artery the wall adjacent to the aortic aneurysm was found to bulge into the lumen of the pulmonary artery (Fig. 2). The volume of the aneurysm was 800 cc. The aortic valves were competent when tested with a column of water in the aorta. There was no communication between the aneurysm and the pulmonary artery.

The remaining viscera showed chronic passive hyperemia.

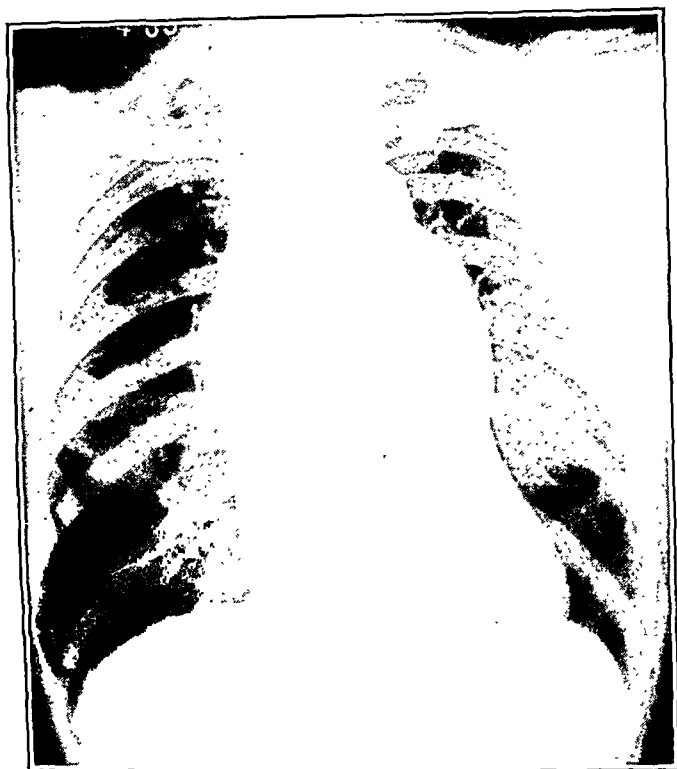


FIG. 1 (Case 1).—Roentgenogram of the chest showing the aortic aneurysm.



FIG. 2 (Case 1).—The wedge points to the pulmonary artery which has been opened. The one wall of the pulmonary artery can be seen to bulge back into the lumen because of the external pressure caused by the aneurysm of the aorta. Note the increased thickness of the right ventricle.

Upon *microscopic examination*, the aorta showed syphilitic mesaortitis. The aortic leaflets were normal. There was evidence of hypertrophy of the right ventricle, and the various viscera showed chronic passive hyperemia.

The final diagnosis was: 1, syphilitic aneurysm of the ascending limb and arch of the aorta with compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, right side (cor pulmonale); 3, myocardial insufficiency with hydropericardium, pleural effusions, ascites, and chronic passive hyperemia of the viscera.

CASE 2.—S. W., a 41-year-old colored laborer, entered Cleveland City Hospital, May 31, 1930. His chief complaint was shortness of breath of 6 weeks' duration. The patient had been in good health until about April 15, 1930, since which time he had had shortness of breath, cough, edema of the feet, and weakness. The patient denied ever having had a penile chancre or rheumatic fever.

Examination showed the patient to be normally developed and well nourished but cyanotic and orthopneic. The jugular veins were distended. There were a few râles at the bases. The left border of the heart was at the anterior axillary line. The cardiac mechanism was normal except for tachycardia. There was a systolic murmur at the second intercostal space to the right of the sternum. The liver was not very tender, but was much enlarged, the edge being at the umbilicus. There was marked edema of the trunk, the genitalia, and the legs. The blood pressure measured in millimeters of mercury was 120 systolic and 90 diastolic.

The urine contained albumin Grade 1. The blood Wassermann test was 4+ on two occasions.

Fluoroscopic and film studies of the chest showed a marked enlargement of the heart, the total transverse diameter measuring 16.9 cm., whereas the total internal diameter of the chest measured 28 cm. The entire aorta was dilated with a definite aneurysm of the first part of the ascending aorta. The lungs showed passive hyperemia.

The electrocardiogram in the conventional leads showed a normal mechanism and right axis deviation.

The patient made temporary improvement with bed rest, digitalis, sedation, and diuretics but finally died of heart failure about 5 months after admission, on November 1, 1930.

The clinical diagnosis was: 1, syphilitic aortitis with aneurysm of the ascending aorta and narrowing of the coronary ostia; 2, cardiac hypertrophy and dilatation; 3, myocardial insufficiency.

AUTOPSY. External examination was negative. The *heart* with the aorta weighed approximately 600 gm. The enlargement of the heart was almost entirely right sided. The trabeculæ carneæ and papillary muscles were strikingly enlarged in the right ventricle and the chamber was markedly increased in size. The trabeculæ carneæ and papillary muscles on the left were of average size and the chamber was not enlarged. Otherwise the heart was normal. The aortic leaflets were normal. The coronary arteries and their ostia were normal.

The *aorta* showed a typical syphilitic aortitis. There was a saccular aneurysm 6 cm. in diameter, located 1 cm. above the commissures. This aneurysm contained a laminated, partially necrotic clot. Externally the aneurysm bulged forward and to the left compressing the pulmonary artery 2 cm. above the valve. The compression was severe and produced a marked stenosis of the pulmonary artery. There was no communication between the lumen of the aneurysm and that of the pulmonary artery.

The *other viscera* showed varying degrees of passive hyperemia.

Microscopic examination of the aorta showed the characteristic lesions of syphilis. Sections of the right ventricular wall showed hypertrophy. The other organs showed chronic passive hyperemia.

The final diagnosis was: 1, syphilitic aneurysm of the ascending arch of the aorta with marked compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, mostly right ventricle (*cor pulmonale*); 3, myocardial insufficiency with chronic passive hyperemia of the viscera.

CASE 3.—J. J., a 59-year-old white laborer, entered Mount Sinai Hospital November 18, 1931. His chief complaint was swelling of the legs of 1 month's duration. He had been in good health until about October 15, 1931, since which time he had had swelling of the legs and ankles, increase in size of the abdomen, and dyspnea on exertion. These symptoms had become progressively more severe. He denied any precordial pain but had had occasional sharp pains in other portions of the chest.

Examination showed the patient to be normally developed and obese, but acutely ill, severely dyspneic, and notably cyanotic. The entire body was edematous. The neck veins were markedly distended. There was dullness to percussion and diminution of the intensity of the breath sounds at both lung bases. The liver was enlarged, and there was moderate ascites. The heart was markedly enlarged in both directions. There was a systolic murmur at the apex and the mechanism was normal. There were no clinical signs of aneurysm of the aorta. The blood pressure measured in millimeters of mercury was 118 systolic and 90 diastolic.

Urinalysis showed albumin Grade 1. The blood Kline test for syphilis was positive.

Fluoroscopic study of the chest showed the heart to be enlarged to the right and the left, the transverse diameter being 16.5 cm. whereas the total internal diameter of the chest was 29.5 cm. There was considerable diffuse dilatation of the aorta, the transverse diameter measuring 9 cm. The lungs showed passive hyperemia.

The electrocardiogram in the conventional leads showed a normal sinus rhythm with marked right axis deviation. There was notching of the QRS complex in all leads.

The patient made temporary improvement on appropriate treatment, but ultimately expired on the 19th hospital day, December 6, 1931.

The clinical diagnosis was: 1, Ayerza's disease; 2, syphilitic aortitis with dilatation.

AUTOPSY. External examination was negative. The heart was considerably enlarged and dilated, weighing 630 gm. The right atrium was not appreciably hypertrophied, but the right ventricle was markedly hypertrophied, the wall measuring 10 mm. in thickness. The left atrium was normal except for dilatation. The left ventricle showed moderate hypertrophy, the wall varying between 10 and 20 mm. in thickness. The heart valves were normal. The coronary arteries and their ostia were normal.

The aorta showed syphilitic aortitis with a diffuse aneurysmal dilatation of the ascending limb, the circumference being 10.5 cm. The dilated aorta compressed the pulmonary artery for a distance of 3 cm. in such a fashion as to lead to a definite constriction of the pulmonary artery. The portion of the pulmonary artery caudad to the stenosed area was dilated but nevertheless was thicker than usual, the wall measuring 2 to 3 mm. in thickness. The aorta showed no evidence of rupture.

The remaining viscera showed chronic passive hyperemia.

Microscopic examination of the aorta showed the typical changes of syphilitic aortitis. The aortic leaflets were normal. Section of the dilated portion of the pulmonary artery showed hypertrophy of the media. Elastic fibers were prominent.

The final diagnosis was: 1, syphilitic aortitis with aneurysmal dilatation and marked compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, mostly right ventricle (*cor pulmonale*); 3, myocardial insufficiency with chronic passive hyperemia of the viscera.

Comment. The following considerations are based on a study of the cases reported in the literature and the cases discussed in this communication.

Etiology. The cases were all presumably due to syphilis. This can be recognized from the gross description of the aorta in the older reports, and from the gross and microscopic findings in the more recent ones.

Frequency. All writers who have described this condition have commented upon its extreme rarity. No doubt the condition is very unusual but it is thought that the paucity of reports may be due to the fact that sufficient attention has not been directed to this entity.

The Aortic Aneurysm. These were located in the ascending arch of the aorta involving either the sinuses of Valsalva or the region just above the commissures. Their size was variable as is illustrated by the 3 cases here reported. In Case 1 the aneurysm was large, involving the entire ascending portion of the aorta and a portion of the arch. In Case 2 the aneurysm was relatively small, no dimension exceeding 6 cm. In Case 3 the aorta showed diffuse dilatation rather than a distinct aneurysm. Most of the cases in the literature describe relatively small aneurysms which brought about compression of the pulmonary artery more because of their location than their sheer size. In all cases the aneurysm bulged anteriorly and to the left, thereby encroaching upon the pulmonary artery.

The Pulmonary Artery. The pulmonary artery showed very definite obstruction in all cases. This was usually due, as in the cases here reported, to invagination of the wall of the pulmonary artery into its lumen. In a few recorded cases the obstruction was caused by a flattening of the pulmonary artery or by a viselike action caused by the aortic aneurysm. Uncommonly, the aorta eroded into the pulmonary artery and blocked its lumen, although there was not communication between the cavity of the aneurysm and the lumen of the pulmonary artery.

The Heart. All cases showed outstanding hypertrophy and dilatation of the right side of the heart, thus constituting in terms of modern terminology a cor pulmonale. None of the cases showed any significant lesion of the aortic valve. In one case the right ventricle was so dilated as to result in a relative tricuspid insufficiency.⁶

Clinical Findings. The aneurysm of the aorta was silent in some instances and in others gave clinical signs of its presence. The signs of myocardial insufficiency and especially of failure of the right side of the heart were evident. Cyanosis was a prominent feature in the cases in which the clinical findings were adequately described. Most of these cases showed a systolic murmur which was in no way diagnostic. Two authors^{5,6} noted the presence of a systolic murmur heard over the back of the chest in the region between the scapulæ. One⁵ felt that this murmur originated in the pulmonary artery at

the point of stenosis. Bufalini² described a systolic murmur and thrill located at the pulmonic area. This murmur was not noted in the cases here reported, although no particular search for its presence was made. In one case⁶ (referred to above) there was clinical evidence of tricuspid insufficiency which at autopsy was found to be due to dilatation of the right ventricle and the tricuspid ring.

Roentgen Findings. Roentgen studies of the chest were made in only a few of the recorded cases. Except for indicating the presence of an aneurysm in such a location that pressure on the pulmonary artery could result, the roentgenologic findings were not unusual.

Electrocardiographic Findings. The only electrocardiograms available in this condition are the ones here reported. Both showed right axis deviation. On theoretical grounds it would seem that right axis deviation should be present almost invariably.

Clinical Course. In all cases reported the course was unfavorable and ultimately fatal.

Clinical Diagnosis. The possibility of an aneurysm causing heart failure by pressing on the pulmonary artery can be considered only if all other causes of heart failure are excluded. The likelihood becomes greater if signs of enlargement and failure of the right side of the heart dominate the clinical picture. Roentgen study is of help in showing that the aneurysm is in such a position that it can press upon the pulmonary artery. In certain cases, roentgenologic study might show enlargement of the right side of the heart. Electrocardiographic evidence of right axis deviation would be corroborative. Under such circumstances the diagnosis can be considered probable. In none of the cases in the literature or in those here reported was the correct etiologic diagnosis suspected antemortem.

Summary. Heart failure due to syphilitic aortic aneurysms is usually caused by dilatation of the aortic valve ring with resultant aortic insufficiency. Heart failure due to obstruction of the pulmonary artery from pressure of a syphilitic aortic aneurysm is an extraordinary occurrence. Three such cases and similar ones previously reported permit the following conclusions:

1. The aortic aneurysm may be large or small. It bulges anteriorly and to the left, thereby compressing the pulmonary artery.
2. The pulmonary artery is obstructed by either simple pressure, a viselike action, or by erosion of the aneurysm into the lumen (without rupture).
3. The heart shows hypertrophy and dilatation of the right side thus constituting in terms of modern terminology a cor pulmonale.
4. Clinically, myocardial insufficiency, especially of the right side of the heart, is evident. The aneurysm may or may not give physical signs of its presence. Roentgen studies show the aneurysm in such a position that it could press on the pulmonary artery and the electrocardiograms reported show right axis deviation. Under such

circumstances and if all other causes of heart failure are excluded, the diagnosis can be considered probable.

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A STUDY OF THE INCIDENCE OF CORONARY OCCLUSION AND ANGINA PECTORIS IN THE WHITE AND NEGRO RACES.

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MOST studies of the incidence of coronary occlusion and angina pectoris have failed to emphasize the relative frequency of these conditions in the white and negro races.^{2,5,10,13} White¹⁹ states that "race, temperament, social and economic status, and occupation appear to have some slight bearing on the incidence of coronary disease," and "the full-blooded negro rarely or never" has angina pectoris. Levy¹² states that in coronary heart disease there is no significant difference in the incidence in the white and colored races, although in his own experience the more advanced degrees of sclerosis are less common in the negro. These two observers, however, fail to mention the relative racial incidence of coronary occlusion *per se*. On the other hand, in those series where the relative racial incidence was studied, striking differences were noted. Schwab and Schulze,¹⁶ in a study of 4252 white patients, found 11 cases of angina pectoris, while a study of 3936 negro patients failed to disclose a single instance of this condition. Hedley,⁷ in a study of 450 fatal cases of heart disease in Washington, D.C., found 34 instances of coronary thrombosis, all being white (30 males and 4 females). Gager and Dunn,⁴ in a study of consecutively chosen records of 1200 cases (white 600, negro 600) of structural heart disease in Washington, D. C., found 20 instances of angina pectoris and 15 of coronary thrombosis in the white group, while in the colored series there were 10 instances of angina pectoris and 2 of thrombosis. Lisa and Ring,¹⁴ in an analysis of 100 necropsy records, selected from

942 necropsies performed at City Hospital, New York, from 1928 to 1931, found a racial incidence of 81 white persons (66 males, 15 females), 18 negroes (16 males, 2 females), and 1 Chinese male. Stone and Vanzant,¹⁷ in a study of 915 consecutive cases of heart disease seen from 1920 to 1926, found 501 to be white and 414 negroes. In this group, angina pectoris occurred in 15 white patients (10 males, 5 females) and in 6 negro females. These authors make no reference to coronary occlusion. Laws,⁹ in a review of 438 patients (white, 237; negro, 201) with arteriosclerotic and hypertensive heart disease, found 16 instances of angina pectoris in the white and 3 in the negro. There was no mention made of coronary occlusion. Johnston,⁸ in a study of 400 consecutive autopsy records, 100 for each sex of each race, found 13 instances of coronary occlusion in the white (9 males and 4 females) and 6 in the negro (4 males and 2 females). The author made no reference to angina pectoris. The lack of sufficient emphasis on the incidence of coronary occlusion and angina pectoris in the white and negro races prompted us to investigate this subject.

Methods and Materials. Our observations were made at Charity Hospital, an institution well adapted for such a study because the admissions of the two races are practically equal. This study includes a review of the case records of patients admitted to the medical service during the last 10 years (1928-1937, inclusive). There were 137,514 during this period, of which 83,231 were white and 54,283 were negroes. Only those records were selected which fulfilled the following criteria:

I. *Coronary occlusion was considered present when:* A. Patients presented the classical history and had had 1 or more of the following manifestations: 1, moderate fever and leukocytosis of short duration; 2, changing electrocardiogram; 3, pericardial friction rub. We have chosen to refer to this group as patients *diagnosed by clinical methods*.

B. *Patients had classic evidence of coronary occlusion.* These patients will be up *diagnosed by electrocardiographic methods*.

C. *Occlusion was found at autopsy.* We referred to this third group as those *diagnosed by autopsy*.

II. Angina pectoris was considered present when the patient presented a history of the classical pain which was relieved dramatically by nitrites.

As a result of the rigid diagnostic criteria, some cases of angina pectoris and coronary occlusion were probably discarded. Nevertheless, in order to obtain significant conclusions, we felt that this was justified, since we were reviewing case histories.

Results (See Tables 1 and 2). *Coronary Occlusion.* We found 162 acceptable records of definite coronary occlusion. Of these, 138 (85.2%), were white (121 males and 17 females) and 24 (14.8%) were negroes (22 males and 2 females). Of the white patients, 44 were diagnosed by clinical methods, 54 by electrocardiographic evidence and 40 by necropsy. Of the negro patients, 2 were diagnosed by clinical methods, 2 by electrocardiographic evidence and 20 by autopsy. In both races the occlusion occurred most frequently during the fifth, sixth and seventh decades. Included with the

white patients is a case of a 56-year-old Indian male who had a posterior infarct.

TABLE 1.—THE RELATIVE INCIDENCE OF CORONARY OCCLUSION IN THE WHITE AND NEGRO RACES.

Negro	White *	Race.	Sex.	Age.						Method of diagnosis.								Season.				Total.
				30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80+.	Total.	Clinical.	E.C.G.		Autopsy.				Autumn.	Winter.	Spring.	Summer.	
												Ant.	Post.	Ant.	Post.	Both.	Unknown.					
	M	8	30	43	31	9	0	121	37	27	23	10	3	3	18	31	39	23	28	138		
	F	1	2	5	7	2	0	17	7	3	1	3	0	0	3	6	5	2	4			
	M	2	7	7	5	0	1	22	1	1	1	7	0	1	11	3	8	6	5	24		
	F	0	2	0	0	0	0	2	1	0	0	0	0	0	1	1	0	1	0			
Total																					162	

* One of the patients included in the white group is a 56-year-old Indian male.

Angina Pectoris. There were 29 (90.7%) cases of angina pectoris in the white race (24 males and 5 females) and 3 (9.3%) in the negro (3 males and 0 females). The greatest incidence of angina pectoris occurred in the sixth decade.

TABLE 2.—THE RELATIVE INCIDENCE OF ANGINA PECTORIS IN THE WHITE AND NEGRO RACES.

Race.	Sex.	Age.							Season.				Total.
		30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80+.	Total.	Autumn.	Winter.	Spring.	Summer.	
White	M	3	4	9	6	2	0	24	5	10	4	5	29
	F	2	1	0	1	0	0	5*	2	2	0	1	
Negro	M	0	1	2	0	0	0	3	0	2	1	0	3
	F	0	0	0	0	0	0	0	0	0	0	0	
Total													32

* Includes 1 white woman whose age was unknown.

Discussion. In the past, the difference in incidence of coronary occlusion in the negro and white races has not been stressed. In fact, some observers state that there is no significant difference.^{13,19} Many studies of coronary occlusion fail to include an analysis of

racial differences.^{5,10,11,20} The studies of Hedley⁷ and Lisa and Ring¹⁴ suggest a relatively low incidence of coronary occlusion in the negro. These findings may be questioned because of the failure of the observers to make allowances for the relatively small negro population where the studies were made. The findings of Gager and Dunn⁴ and Johnston⁸ are corroborated by our studies: we found 138 white patients and only 24 negroes with coronary occlusion (see Table 1). When a correction is made for the difference in the medical admissions for the 2 races, we obtained a ratio for coronary occlusion of 7 whites to 2 negroes. These findings tend to be significant, as the cases were selected under similar circumstances with practically equal negro and white admissions.

In contrast to the above differences of opinion in regard to coronary occlusion, the observers uniformly agree that the incidence of angina pectoris in the negro is rare.^{9,16,17,19} We found this to be true in our studies. We were able to collect 32 cases of angina pectoris, of which 29 were white and 3 negro (see Table 2). In no instance was angina pectoris found in the negro female. We eliminated those patients in whom luetic aortitis was suspected. Of the 32 patients with angina pectoris only 1 had a positive Wassermann. Subsequent clinical and laboratory observations failed to disclose any signs of aortitis in this patient.

Any explanation for the low incidence of coronary occlusion and angina pectoris in the negro can only be conjectured at this time. Coronary occlusion and angina pectoris, along with other cardiovascular states such as hypertension, have been associated with high tension living conditions and occupations requiring considerable responsibility and intelligence, *e. g.*, the physician, banker and lawyer. However, it has been shown recently in the South that hypertension is more prevalent in the negro than in the white,^{1,15,18} while coronary occlusion and angina pectoris are uncommon. Likewise, as pointed out by Schulze and Schwab¹⁵ and Weiss and Prusmack,¹⁸ it is doubtful that the American negro is as placid and phlegmatic as is commonly supposed. An evaluation of the effect of nervous tension on these conditions becomes more difficult when one considers hypertension in the African, as contrasted with the American, negroes. Civilization probably has had its effect upon the nervous state of the American negro, producing greater nervous tension than is found in the African. Hypertension is rare in the latter and very common in the former, while the incidence of coronary disease is relatively low in both.³ These conflicting observations cast doubt upon the significance of psychogenic factors influencing the incidence of coronary occlusion and angina pectoris in the white and colored races.

Physical effort apparently has no effect upon the difference in incidence of these diseases in the two races, for the patients in our series were laborers who, as a rule, did equally strenuous work. These

findings, however, are in contrast to those of Levine and Brown,¹⁰ who state that physical effort is conducive to coronary thrombosis, although they did not mention a racial difference. It is interesting to note that physical effort was essentially the same in both races of our series. However, angina pectoris, a syndrome precipitated by physical effort, was rarely observed in the negro. This suggests that, although physical effort is significant as a precipitating cause of the pain of angina pectoris, it apparently is of little importance as a primary etiologic factor. The low incidence of coronary occlusion and angina pectoris in the female, as compared to the male, might be considered as evidence favoring the idea that physical effort is conducive to the occurrence of these conditions. This is open to question, however, as there probably are unknown factors of sex relationship not associated with physical effort influencing the incidence.

As mentioned by Weiss and Prusmack¹⁸ in their studies of the incidence of hypertension, the relatively low incidence of angina pectoris in the negro as compared to the white may be partly explained on the basis of the following factors: 1, the lack of intellectual ability to interpret fully and describe the sensation of pain; 2, the distress of myocardial, cerebral or renal failure symptoms, which often obscures all history of angina pectoris; and 3, the fact that uncomplicated anginal type of heart failure usually occurs in an ambulatory patient. It is doubtful, however, that such factors could account for more than a small part of the difference between the 2 races. It is more than likely that there is a genuine difference in racial incidence, the cause or causes of which might throw light upon a more thorough understanding of the etiology and pathogenesis of angina pectoris as well as coronary occlusion.

Summary. A study of the medical case histories at Charity Hospital of Louisiana from 1928 through 1937 revealed a relatively low incidence of coronary occlusion and angina pectoris in the negro as compared with the white race. Of 162 instances of coronary occlusion, 138 (85.2%) were white (121 males and 17 females), and 24 (14.8%) were negro (22 males and 2 females); of the 32 instances of angina pectoris, 29 (90.7%) were white (24 males and 5 females) and 3 (9.3%) were negro (all males). After the data were corrected for the differences in admission, the ratios of white to negro for the incidence of coronary occlusion and angina pectoris were found to be 7 to 2 and 4 to 1, respectively. Some of the factors which might influence the incidences of the two diseases in the white and negro races were discussed.

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EXPERIMENTAL LOCALIZED AURICULAR NECROSIS.

AN ELECTROCARDIOGRAPHIC STUDY.*

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AURICULAR electrocardiographic changes occurring in coronary disease have been studied by a number of investigators, and altered auricular complexes of this type have been seen from time to time in electrocardiograms in the Heart Station files. Master⁷ reported changes in the *P* wave in 32 of 40 cases of acute coronary artery occlusion. These changes consisted of increased amplitude, notching or widening and were attributed to auricular dilatation. Inasmuch as the changes occurred most frequently in Leads I and II, left auricular dilatation was presumed to be the cause. Lambert,⁵ in correlating similar electrocardiographic findings in patients with experimentally induced auricular infarction in rabbits, concluded that such changes were the result of impaired auricular coronary circulation comparable to those in ventricular coronary insufficiency. Vela¹³ reported a case with inversion of the auricular complex during an attack of angina pectoris followed by a return to normal contour after the attack. Condorelli² was unable to obtain alterations in the configuration of the auricular complex or the *P-Q* interval by temporary occlusion of the ascending auricular branch of the right coronary artery. Analysis of the records of Parkinson and Bedford¹⁰ dealing with ventricular *S-T* changes in coronary thrombosis shows notching, inversion and abnormal amplitude of the *P* wave. Reginier and Lambert¹¹ reported 3 cases of acute ventricular infarction in which inversion, reduplication and diminution in the *P* waves occurred. Abramson, Fenichel and Shookhoff,¹ in an experimental study on dogs and cats, observed elevation of the auricular *S-T* segment in Lead I in cases of circumscribed necrosis of the left auricle, and depression of the same segment in right auricular

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necrosis. Depression of this segment occurred in Leads II and III without regard to the location of the necrotic area. In a case of arteriosclerotic heart disease with complete heart block, Nathanson⁹ has observed an auricular complex in Lead III consisting of a deep auricular Q wave, an elevation of the auricular S-T segment with upward convexity and an upright T_a wave, comparable to changes occurring in the ventricular complexes in coronary thrombosis. Feil and his associates^{3,4} have reported careful postmortem studies of 10 cases of auricular infarction. The right auricle was involved in 2; auricular fibrillation with frequent ventricular extrasystoles was noted in 1, and sinus rhythm, sinus arrest, ventricular escape, and a prolonged P-R interval was seen in another. Maher⁶ observed a thrombus in the right auricle involving the region of the sinus node in a case of coronary sclerosis presenting sino-auricular block. This brief survey of the pertinent literature indicates that auricular coronary insufficiency and infarction do occur and may be associated with changes in cardiac rhythm and in the contour of the auricular complex.

This study was undertaken to observe the effect of experimentally induced circumscribed auricular necrosis upon this complex in an effort to gain further insight into the mechanisms responsible for its occurrence.

Method. Auricular necrosis was induced in 57 areas of 22 dogs by the intramural injection of 95% alcohol. Of these, 6 were induced in the left auricle; 16 in the left auricular appendage; 24 in the right auricle; and 9 in the right auricular appendage. Inasmuch as localized appendicular necrosis yielded results similar to necrosis of the auricle proper, the designation of right and left auricular necrosis will be used in all cases. The injections in 37 areas were preceded by the mechanical induction of A-V block, which enabled detailed comparison of the auricular S-T segment and auricular T wave. The Meakins⁸ method of inducing A-V block was used: 2 blades of a clamp were introduced into the heart on either side of the interventricular septum and the common A-V bundle was clamped. The usual limb leads were used, at times with a sensitivity of the string greater than customary. In addition, an esophageal lead was used, the electrode being placed in the esophagus at the level of the auricle. A No. 1 Hindle string galvanometer was used. Control records before and after application of the clamp were obtained in each case prior to the induction of the circumscribed necrosis. All tracings were obtained with the chest open and the pericardium removed.

Results. Of the 20 instances of induced auricular necrosis not preceded by the induction of A-V block, changes occurred in 10, 7 resulted in a nodal rhythm; 1 in a paroxysmal auricular tachycardia; and 2 in a wandering pacemaker. These arrhythmias resulted from localized necrosis of the right auricle in the region of the sinus node.

Of the 37 produced following mechanical A-V block, changes occurred in 30; 2 resulted in intra-auricular block represented by unusually tall, broad, slurred and notched auricular complexes

(Fig. 1). These resulted from involvement of the left auricular appendage at its cephalic margin and point of junction with the auricle proper near the interauricular septum. Of the remaining 35, particular attention was given to the auricular *S-T* segments and *T* waves. Outstanding changes, which occurred in 28, were elevation of the *S-T* segment with upward bowing similar to changes occurring in the equivalent segment of the ventricular complex in ventricular wall infarction. This was associated with the development of an auricular *Q* wave in all instances.

The observation that of 14 left auricular areas of necrosis producing such auricular *S-T* changes, 10 resulted in an elevation of this segment with upward bowing in Lead I, with an associated auricular *Q* wave (Fig. 2, *a*, *b*) aided in localizing the necrosis. At the same time a depression of the auricular *S-T* segment occurred in the other leads. In 4 other instances the same type of change, more marked in degree, occurred in the esophageal lead with minimal changes in the other leads (Fig. 3). In the 14 cases of right auricular involvement which produced auricular *S-T* deviations, Lead I was not so affected. The *S-T* changes appeared in Leads II and III, and quite markedly in the esophageal lead in all cases (Fig. 4). In these instances, the changes were similar to those occurring in Lead I with left auricular necrosis. Inverted auricular *T* waves in Lead I occurred in 2 cases soon after localized left auricular necrosis (Fig. 5) without previous *S-T* elevation.

In the auricular initial complex (*P* proper) changes frequently consisted of diminution (in 18) or increase in its amplitude (in 8), combined with slurring (in 9), notching (in 9), broadening (in 3), inversion (in 7), and the development of a *Q* wave in 28 and a broad *S* wave in 5. Except for the correlation regarding the *Q* waves mentioned above, changes of these types could not be correlated with the location of the necrosis. An *M* or *W* shaped initial auricular complex appeared in Lead I after left auricular necrosis in 1 instance, and in the third and esophageal leads after right auricular necrosis in another.

LEGENDS FOR FIGS. 1 AND 2.

FIG. 1.—(*a*) Control, esophageal lead, E, and Lead III. (*b*) Intra-auricular block shown by prolongation of *P* wave with gross slurring and decreased amplitude resulting from localized necrosis in left auricular appendage, cephalic margin, near junction with left auricle proper and near interauricular septum. (Mechanical A-V block induced prior to control record.) Standardized 1.5 cm. = 10 millivolts.

FIG. 2.—(*a*) Control, esophageal and three standard leads. (*b*) Development of auricular *Q* and elevation of auricular *S-T* with upward bowing in Lead I, resulting from localized necrosis of left auricle. (*c*) One hour later, apparent evolution with loss of auricular *Q*₁, development of auricular *Q* in Leads II, III and esophageal lead, inverted auricular *T*₁, elevation of auricular *S-T* in Leads II, III and esophageal lead. (Mechanical A-V block induced prior to control record.) Standardized 1.5 cm. = 10 millivolts.

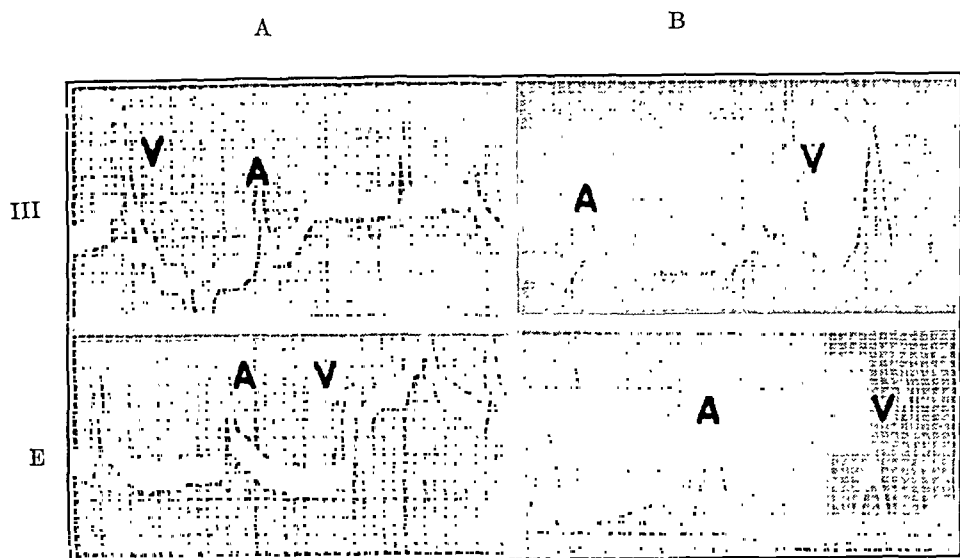


FIG. 1

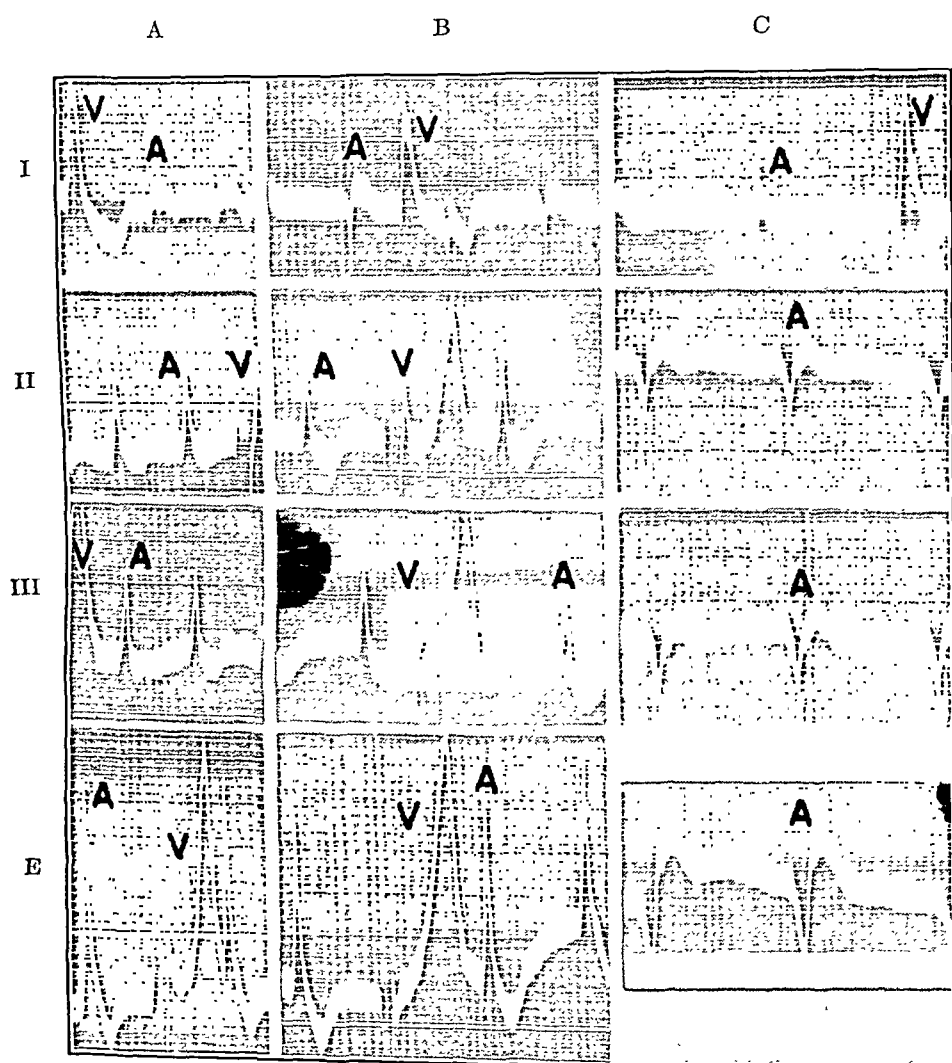


FIG. 2

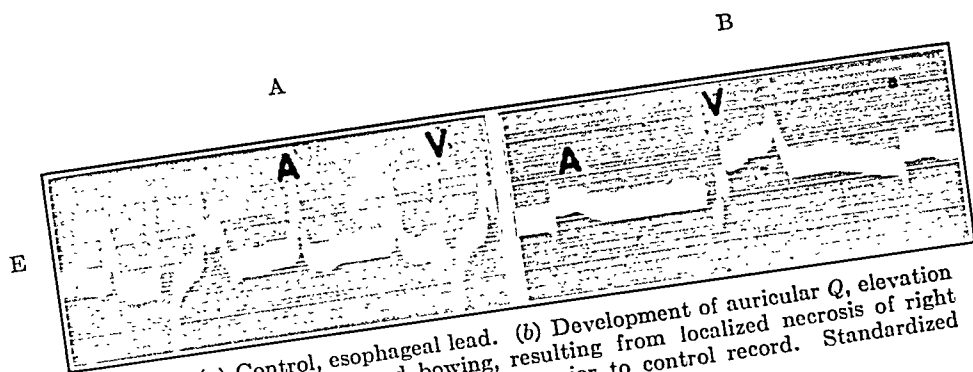


FIG. 3.—(a) Control, esophageal lead. (b) Development of auricular Q, elevation of auricular S-T with upward bowing, resulting from localized necrosis of right auricle. (Mechanical A-V block induced prior to control record. Standardized 1 c.m. = 10 millivolts.

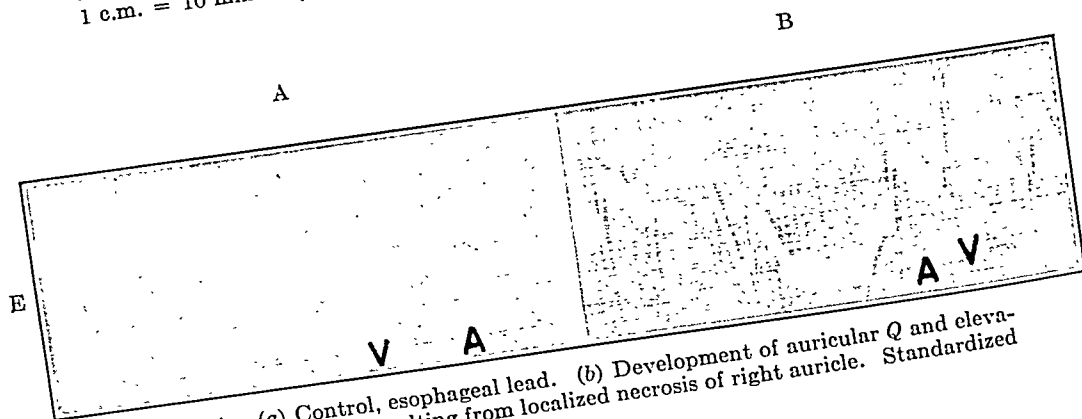


FIG. 4.—(a) Control, esophageal lead. (b) Development of auricular Q and elevation of auricular S-T resulting from localized necrosis of right auricle. Standardized 1.5 cm. = 10 millivolts.

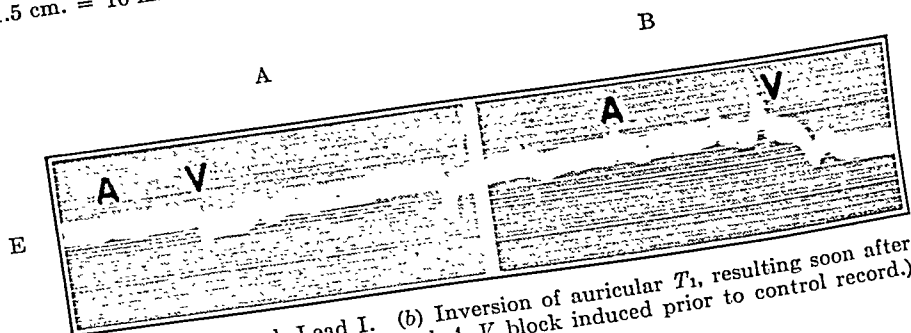


FIG. 5.—(a) Control, Lead I. (b) Inversion of auricular T₁, resulting soon after necrosis of left auricle. (Mechanical A-V block induced prior to control record.) Standardized 1 cm. = 10 millivolts.

A definite evolution of the auricular $S-T$ changes was demonstrated in only 1 experiment in which an area of left auricular necrosis had been induced. The typical elevation of the auricular $S-T_1$ segment gave way to an inverted auricular T_1 followed by a restoration of the $S-T$ segment, and a loss of the auricular Q_1 over a period of an hour. At the same time, deep auricular Q waves as well as an elevation of the auricular $S-T$ segment and upright T_a wave were seen in the second, third and esophageal leads (Fig. 2, *a*, *b*, *c*). The ventricular complexes did not change in direction, the electrodes had not been altered, and the position of the heart did not appear changed during the period.

Non-specific changes occurred in the ventricular complexes in 11 instances. In 16 cases of definite localized auricular necrosis, electrocardiographic changes did not occur.

Discussion. The results of our experiments appear to substantiate the observations of other workers. The auricular $S-T$ segment is usually obscured in clinical electrocardiograms by the ventricular complex and its actual deviation in impaired auricular coronary circulation cannot always be clearly observed without the use of the esophageal lead. The possibility that superimposition of an altered auricular $S-T$ segment upon any portion of the succeeding ventricular complex may produce minor changes in the latter (see Fig. 2, *b*) must be considered. Occasional cases of so-called angina pectoris with slight changes in the ventricular complex or its $S-T$ segment may actually be due to auricular infarction with changes in the auricular T and $S-T$ segments which by superimposition lead to these variations.

In general, our criteria for localization of left auricular necrosis are similar to those of Abramson and his associates.¹ At times, however, instances of left auricular involvement produced auricular $S-T$ elevation only in the third and esophageal leads. Further, in localization of right auricular involvement, we observed elevation of the auricular $S-T$ segment in Leads II and III with marked changes of this type in the esophageal lead. Changes in Lead I usually consisted in diminished amplitude of the auricular QRS complex with little effect upon the $S-T$ segment.

Our failure to observe changes in the auricular complexes in all cases of induced auricular necrosis is probably due to the presence of silent areas in the auricular appendages or possibly to the selection of superficial muscle bundles by the injected alcohol, to the exclusion of the deeper ones. Elevation of the auricular $S-T$ segment in the second, third and esophageal leads appearing in some cases of left auricular necrosis may be dependent upon selective involvement of only part of the wall by the alcohol injected into the apparently similar area on different occasions. Such variations and the absence of changes on some occasions may possibly be explained by the work of Robb and Robb.^{12a,b} Definite changes were noted in the esopha-

geal lead in some cases where they did not occur in the standard leads.

We believe that cases of angina pectoris or coronary thrombosis which give evidence of, 1, arrhythmias of auricular origin, 2, definite changes in the auricular complex, or, 3, only inconsiderable changes in the ventricular complexes, should be suspected of either impaired circulation to, or infarction of, the auricles. This may occur as the only lesion or in combination with ventricular involvement.

Summary. 1. The effect of localized auricular necrosis upon the electrocardiogram of the dog was studied, to help elucidate the changes in the auricular complex and minor changes in the ventricular complex occurring in coronary disease.

2. Necrosis near the sinus node resulted in a nodal rhythm, wandering pacemaker, auricular extrasystoles and paroxysmal auricular tachycardia.

3. Localized left auricular necrosis frequently produced elevation of the auricular *S-T* segment in Lead I with an upward bowing and an auricular *Q* wave. In 2 instances, intra-auricular block resulted.

4. In a few instances of left auricular necrosis, similar auricular *S-T* changes occurred in the esophageal lead, to the exclusion of Lead I.

5. Right auricular necrosis produced similar auricular *S-T* changes in the esophageal lead and in Leads II and III.

6. Changes in the initial auricular complex (*P* wave proper) consisted of broadening, inversion, diminution or increase in amplitude, and slurring, notching, the development of a *Q* or *S* wave, or *M* or *W* shapes.

7. Some cases of localized auricular necrosis failed to alter the electrocardiogram, while others produced minor changes in the ventricular complexes.

8. The similarity of such induced areas of localized auricular necrosis to clinically occurring auricular infarction was considered, and the possible clinical import of the results discussed.

I am indebted to Dr. L. N. Katz, under whose guidance this work was done, and to Dr. W. A. Brams for their interest and many helpful suggestions, and to Miss E. Lindner and Mr. K. Jochim for invaluable technical assistance.

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METRAZOL CONVULSIVE SHOCK THERAPY IN AFFECTIVE PSYCHOSES.

A FOLLOW-UP REPORT OF RESULTS OBTAINED IN SIXTY-ONE DEPRESSIVE AND NINE MANIC CASES.*

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In February, 1938, before the Missouri-Kansas Neuropsychiatric Association, I presented a preliminary report¹ of results obtained in 10 consecutive severe depressive psychoses by convulsive shock therapy. At that time I could find practically no reports in the literature indicating that the method had proved useful in other hands. I had overlooked a report of Wahlmann,²⁰ who, in 1936, stated that 1 manic depressive patient showing catatonic manifestations had obtained marked improvement after three shock injections. He concluded that the tendency to spontaneous remissions of this disorder argued against the specificity of the treatment.

Prior to publication of my report, Low *et al.*¹³ reported on 16 patients with manic depressive psychoses—5 in the manic stage, 9 depressed, and 2 in the involutional period. In spite of the fact that the illness had lasted for more than 2 years in 6 of their patients, 5 got well. They concluded that in manic depressive psychoses treated with metrazol the rate of recovery does not depend upon the duration of the attack, as in schizophrenia. In comparing the treatment with prolonged narcosis, they felt shock therapy was definitely superior.

Since these reports, many others have confirmed the value of shock therapy in terminating severe depressive stuporous affective reactions. Verstraeten¹⁹ reported favorable results in 3 depressed cases, but stated that manic patients react less favorably and he was disappointed in his results in schizophrenia. Goldstein, Dombrowski, *et al.*,⁶ in a report on treatment of schizophrenia, included 1 depressed and 3 manic patients, but did not give specific results. Wyllie,²³ reporting from Scotland, treated psychoses other than schizophrenia. Two chronic depressed patients were much relieved and certain manic depressives, especially the stuporous cases, reacted very favorably, in his opinion. Kay,¹² treating 7 manic and 2 depressive patients, was able to relieve 3 manic states and the 2 depressed patients promptly. These results led him to feel that

* Presented before the Central Neuropsychiatric Hospital Association, Chicago, Ill., March 17, 1939. Presented by title before the American Neurologic Association, Atlantic City, June 7, 1939.

certain patients with affective psychoses react favorably and almost immediately to metrazol; that treatment of such patients is justified by material reduction of the duration of illness.

Mader¹⁴ reported improvement in over 70% of 61 depressive patients, with one death in the series, which he did not attribute to treatment. He stated that many of his improved cases were practically cured, that very few depressives were uninfluenced by the treatment, and that long duration of illness did not affect prognosis as in schizophrenia. His best success was in the climacteric or involutional group, his poorest results with those showing profound anxiety or compulsive features. He concluded that the chief value of convulsive shock therapy in depressive states is to shorten the duration of illness.

Winn²¹ reported 1 involutional depression of 2 years' duration with good recovery. Serko¹⁷ reported 2 manic depressives with complete remission. Harris,⁹ after treating 18 depressives of stupor type, reported complete recovery or improvement, even when evidence of deterioration seemed present. He recommends metrazol treatment for every case of stupor, regardless of duration; even if complete remission is not obtained, difficult psychiatric nursing problems such as forced feeding can be eliminated.

Cook² reported favorable results in 4 acute manic patients and 5 psychotic depressives. Of the latter, 1 relapsed to a slight degree, 1 became hypomanic. He was also impressed by results obtained with 3 hysterical patients, 1 ill for 12 years. He concluded that stuporous reactions are more favorably influenced because there are fewer dissociation phenomena than in schizophrenia. The abstraction from reality breaks down in the depressive reactions, and after the morbid affect clears, psychotic ideas and abnormal behavior evaporate.

Young and Young²⁴ in a recent article reported results obtained in 21 depressive patients, with improvement in all but 1. They likewise found best results in the chronic midlife stupor states. Read and others¹⁶ reported a study of 49 manic depressives, 27 in manic phase, 13 depressives, 9 mixed. They concluded that metrazol is a valuable aid in treatment of functional psychoses.

As a result of my continued favorable experience with the use of convulsive shock therapy in both the depressive and manic phases I have followed up 70 patients: 61 depressive and 9 manic excitement states. The study of these patients over a period of time adequate to permit evaluation of results forms the basis of this report: particularly the permanency of recovery, the incidence of relapses, and refinements of therapy developed to prevent serious complications.

In my original report, I speculated on the psycho-physiologic reactions of shock therapy upon the emotional reactions of the individual. Since that time scientific evidence has accumulated to

give a more comprehensive theory as to the mechanism through which convulsive shocks improve the psychotic reactions. von Meduna and Friedman¹⁵ attribute the benefits to stimulation or irritation of the whole central nervous system so extensive that mental barriers to certain thought processes are broken down, allowing these thought processes to be carried on properly. This seems very hypothetical and begs the point as far as explaining the reversal in feeling tone that is so characteristic of patients receiving this therapy. Gellhorn,⁴ Gerard,⁵ Himwich,¹¹ Hartman,¹⁰ and others believe the fundamental influence of convulsive shock therapy, as well as of hypoglycemic shock, is through the production of cerebral anoxia: First, a deprivation of oxygen producing a powerful sympathetic stimulation; and secondarily, an opening up of cerebral capillaries, increasing oxygenation to the cerebral cells, thus enabling them to carry out their function more or less normally. Himwich¹¹ and Wortis²² have shown during the marked period of apnea of the convulsive cycle that available oxygen for brain metabolism is markedly reduced.

Whether organic changes in the brain occur from repeated convulsive shocks is still unsettled. There is as yet no good experimental or necropsy evidence available to settle this point. Strecker¹⁸ showed that repeated convulsions in rabbits produce capillary hemorrhages. A few experimental animals have shown other hemorrhagic tendencies. A few necropsy reports on humans have not confirmed this possible danger. However, clinically one notices that patients who have had a number of treatments complain of haziness of memory and relatives report that for some weeks following cessation of treatment patients show mild personality changes, amnesia, difficulty in recalling names, and so on, that suggest mild sensorium changes. There is some reason to believe the good therapeutic results occur from the organic changes produced by the confusional state induced by the convulsion. I have called attention elsewhere to the fact that the results obtained by shock therapy are strikingly similar to those reported from frontal lobotomy by Freeman.³ He believes results occur because of organic brain changes producing a confusional state that breaks up obsessive thinking and thus patients are unable to worry.

Because of the possibility of producing permanent cerebral damage, especially in the involutional and presenile group, I have used as few shocks as possible and would rather run the risk of occasional relapses from insufficient treatment than slow up the intellectual functions of the patient or possibly produce permanent personality changes.

My experience with patients over 45 years of age still indicates that the method is quite safe in this age group. Repeated electrocardiographic studies on all patients past 55 years, some complicated by mild hypertension, some with actual coronary artery disease, have

as yet shown no apparent permanent cardiac defects from convulsive shock therapy. Dr. Willis D. Wright, who made the cardiac studies, has summarized the findings in this group as follows: Electrocardiograms were taken upon 40 depressed patients, aged 45 to 68 years. Of these, 34 patients had no clinical evidence of heart disease. The remaining 6 patients had definite heart disease, including 1 case of rheumatic heart disease with mitral stenosis showing no history of congestive failure; 1 congenital heart disease; 2 hypertensive heart disease; and 2 arteriosclerotic heart disease, 1 of these showing right bundle branch block. Five had suggestive but no conclusive evidence of coronary artery disease. In none of these patients was the original electrocardiographic pattern changed permanently by shock therapy. Repeated electrocardiographs following treatment demonstrated an abnormality in only 1 patient, an *A-V* block that persisted for 2 days.

In my original report, over one-third of the patients were past 55 years. We have had no complications arising from metrazol therapy in the older depressive group. In a few patients, treatment was discontinued temporarily because of intercurrent infections, but later resumed with good effect. My observation up to date does not conform to the absolute contraindications laid down by von Meduna and Friedman¹⁵ in the use of this therapy.

The incidence of mechanical complications is undoubtedly higher than previously suspected and undoubtedly occurs more frequently than suspected. I have had 4 known fracture complications in about 1000 treatments, all in younger patients. Two were chronic schizophrenic patients and 2 had chronic depressions. Persistent back pains after shock therapy are probably the result of spinal fractures. Dr. W. R. Hamsa and myself⁸ have recently reported upon traumatic complications from shock therapy, explaining the mechanism of production as comparable to fractures in tetanus and recommending preventive treatment. These complications are a serious drawback to the therapy and are one reason why its use should be restricted to serious psychotic states and to psychiatric hospitals in experienced hands. I consider metrazol therapy more hazardous than hypoglycemic shock.

As a routine procedure to prevent spinal and leg fractures, a spinal anesthetic of 10 mg. of pontocaine hydrochloride,* or 100 mg. of novocaine is given 1 hour before the metrazol injection. The anesthetic is dissolved in 4 cc. of spinal fluid obtained by a puncture between the first and second lumbar vertebrae by means of a 22-gauge needle and reinjected slowly intraspinally. This gives a transient anesthesia with complete sensory and motor paralysis of all the thoracic and lumbar segments. Since shock therapy is given every 3 days for about 5 to 8 injections in affective psychoses,

* We are indebted to the Winthrop Chemical Company for furnishing Pontocaine for investigative purposes.

the spinal anesthetic offers no serious drawback to treatment. At the onset of the tonic spasm both arms are held adducted against the chest. The greatest problem in complications is the possibility of fracture. Persistent backache should call for immediate radiologic examination.

In certain patients who are very apprehensive, we induce hypoglycemic shock first and at the onset of coma administer metrazol, immediately followed by intravenous hypertonic glucose. We have had no mechanical complications with this combined therapy. The tetanic spasm seems less severe after insulin shock has set in and this fact probably helps prevent fractures. In other patients fearful of the treatment, small doses of scopolamine, grains $\frac{1}{150}$ or $\frac{1}{100}$, given 1 hour before metrazol injection, are quite helpful in allaying anxiety and often make the patient totally amnesic to the individual treatment. We have found that many physicians inadvertently have frightened patients with potential danger of the therapy and have thus caused difficulty of treatment unless some such measure is adopted. We have not found that the use of scopolamine necessitates a larger dose of metrazol. We no longer use alkalization, having become convinced the convulsive threshold is not lowered by its use.

Following the observation of Hall and Leibel⁷ that experimental animals go into convulsions with one-half to one-fourth the usual dose of metrazol after the administration of adrenalin, we have frequently used adrenalin on patients apparently requiring large doses. By giving $\frac{1}{2}$ cc. of adrenalin intravenously, and at the moment of facial blanching, injecting metrazol, we have found that a good convulsive shock will result from half the usual dosage. This reduction we feel is an advantage because of less post-treatment nausea.

I am still inclined to repeat the initial injection plus 1 cc. immediately following the first injection if the patient has failed to have a convulsion. After a second failure I usually wait until the following day, unless the patient is very agitated or excited. We prolong the period of apnea by closure of the mouth and nose at the end of the convulsion for 30 to 60 seconds, as suggested by Freeman.

Although a good many psychiatrists recommend the therapy as applicable to home, office or general hospital management, I still disagree. Since the management of affective disorders is a difficult psychiatric procedure, it should, in my opinion, be administered only in well equipped psychiatric departments in the hands of experienced psychiatrists and psychiatric nurses. In several cases brought to my attention, patients in whom ambulatory treatment was attempted have refused further treatment and upon relapse their fears have driven them to suicide. It takes an unusual degree of rapport between doctor and patient to influence the patient to keep returning for repeated injections. Under strict psychiatric supervision these panic reactions are readily controlled and in no instance

have we had to discontinue treatment because of uncoöperativeness of the patient. Furthermore, while rapid termination of the affective disorder is the rule with shock therapy, efficient psychiatric nursing, psychotherapy, and other psychiatric treatment are very essential and can only be carried out in a closed department. We have also found that the interference of family, relatives and friends is a great deterrent to successful outcome, and thus no visit is permitted while the patient is under treatment. Disregard of these factors makes for poor results and increased frequency of relapses. We have found that it is advisable to hold the patient at least 2 weeks after the last shock, to be certain that the patient is ready to start social rehabilitation. The problem of personal situational factors on the patient's return to his previous environment is of extreme importance and requires prolonged follow-up educational psychotherapy of the family and associates, in order to increase the permanency of the results.

In Table 1, the results obtained in both the depressive and manic patients treated up to date are evaluated.

TABLE 1.—RESULTS OBTAINED IN AFFECTIVE DISORDERS BY CONVULSIVE SHOCK THERAPY. (70 CASES—61 DEPRESSIVE AND 9 MANIC STATES.)

Diagnosis.	No. of cases. Sex.	Age.	Duration of psychosis.	Average shocks.	Days under treatment.	Time followed.	Result.* Relapse.
Reactive depression	16 11 F 5 M	27-67	2 mos.-1½ yrs.	6.5	23	3 over 1½ yrs. 1 over 1 yr. 5 over 6 mos. 7, 3 mos.	9 A 7 B 2 (1 suicide)
Manic depressive: depressed	21 9 F 12 M	29-65	1 wk.-6 yrs.	5.7	18	4 over 1½ yrs. 6 over 1 yr. 3 over 6 mos. 8, 3 mos.	10 A 11 B 3 (1 recovered second course)
Involuntional melancholia	24 14 F 10 M	42-68	1 wk.-3 yrs.	6.5	21	3 over 1½ yrs. 9 over 1 yr. 4 over 6 mos. 8, 3 mos.	11 A 12 B 4 (2 recovered second course) 1 C
Manic states	9 7 F 2 M	26-53	1 wk.-9 mos.	4	16½	1 over 1½ yrs. 3 over 1 yr. 3 over 6 mos. 1, 3 mos.	4 A 4 B 2 (1 recovered second course) 1 C (died)

* Result: A = Complete remission with full insight; return to former social level.

B = Social remission, able to adjust at home but with some residual symptoms, usually anxiety. Incomplete insight.

C = Unimproved; relapses all occurred in B group.

Summary of Treatment Results. Of 61 depressed patients, 28 (45%) have obtained a full remission lasting from 3 to 18 months; 32 (52%) obtained a social recovery; but 7 (11%) relapsed. Four of these were improved again with a second course of treatment; 1 remained unimproved; and 1 committed suicide. Fifty-seven (90%) of the 61 patients, obtained rapid improvement with termination of the depression by metrazol shock therapy. Over 50% of these patients were past 45 years and 42% were past 55; the oldest

was 68. Four of these patients were chronic state hospital patients of from 1 to 6 years' duration.

Four (44%) of 9 manic states obtained a full remission lasting from 3 to 18 months; 4 (44%) obtained a social remission, but 2 relapsed, 1 recovering subsequently and 1 dying of intercurrent infection while under treatment.

The average number of shocks given every 2 to 3 days for the depressives was 6 to 7, with an average period of 3 weeks under treatment; the average number of treatments for the manics was 4, the average duration $16\frac{1}{2}$ days. One case of depression of 6 years' duration gave a classical depressive history, but exhibited the behavior of a catatonic with continuous stupor for 6 years.

Conclusions. 1. Convulsive shock therapy, in spite of certain hazards, is an indicated therapy in chronic depressive and manic affective states.

2. Ninety per cent of severe depressive reactions are terminated within 2 to 3 weeks' treatment.

3. Therapy is most effective in the midlife and presenile depressions. It has proved to be a safe procedure in the older group.

4. Two-thirds of the severe manic states can likewise be terminated by convulsive shock therapy.

5. Convulsive shock therapy should only be given in well equipped psychiatric departments.

6. Spinal and lower extremity fractures are common complications. These can be prevented by administration of a spinal anesthetic prior to shock therapy.

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METABOLIC AND CARDIOVASCULAR EFFECTS OF INTRAMUSCULAR INJECTIONS OF ADRENALIN AND OF AMPHETAMINE.

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THE reports that fatigue is influenced by adrenalin⁷ and amphetamine⁸ have led us to compare the effects of these sympathomimetic drugs on the utilization of carbohydrate, the concentration of sugar and lactic acid in blood and of acetone bodies in blood and urine, the oxygen consumption, the acid-base balance, the pulse and the blood pressure. Four normal fasting men were studied over 4-hour periods while reclining quietly on a bed.

In one series of experiments no drug was administered; 2 subjects who were unacquainted with the plan received intramuscular injections of physiologic saline. After an initial rest of 30 minutes, capillary blood was collected at 15-minute intervals for sugar and lactic acid determinations. At less frequent intervals, venous or arterial blood was drawn for acid-base studies. The subject was connected with an open circuit metabolism apparatus and expired air was collected continuously for $3\frac{1}{2}$ hours, allowing 1 minute every $\frac{1}{4}$ hour for drawing samples and emptying the gasometer. Pulse and blood pressure were observed frequently.

In other experiments, the drug was injected intramuscularly after preliminary observations lasting about 1 hour. One milligram of adrenalin chloride (Parke Davis & Co.) in 0.1% solution or 20 mg. of amphetamine sulphate (Smith, Kline and French Lab.) in 2% solution was used. In some instances, arterial blood was drawn for gas analysis just before injection of the drug and again at the conclusion of the experiment. At least a week elapsed between experiments on a given subject.

Carbohydrate Utilization. The estimation of the utilization of carbohydrate is complicated when the accumulation of a fixed acid such as lactic displaces carbon dioxide from body reserves of bicarbonate. It is on this account that observed increases in the R.Q. shortly after injecting adrenalin have not been accepted as evidence for greater utilization of carbohydrate. Analyses by Cori and Cori² of liver and muscle in rats gave the first proof that adrenalin may,

but does not necessarily, lead to an increase in oxidation of carbohydrate. It mobilizes muscle glycogen "*and it depends on the metabolic state of the animal (presumably on the insulin content of the tissues) to what extent the glycogen mobilized in the muscles is being oxidized.*" We emphasize this conclusion because some have the impression that adrenalin effects a reduction in carbohydrate oxidation. For example, it has been suggested by Himwich and Fulton⁶ that fat is the fuel of emotion, and Cameron¹ has been criticized in his discussion of adrenalin hyperglycemia for not taking into account preferential burning of fat. The principle of our procedure is the same as that employed a few years ago⁴ in an investigation of adrenalin effects on energy exchange in exercise: the measurements were made over the entire period of formation and removal of excess lactic acid.

Sufficient time was allowed for completing the cycle of lactic acid formation and removal (Fig. 1). The final values for blood lactate ranged from 8.9 to 14.7 mg. %, averaging 12 in the control experiments, and from 10 to 17.8, averaging 12.8, about $2\frac{1}{2}$ hours after adrenalin injection. There is no evidence of any effect of amphetamine on blood lactate under the experimental conditions.

The corresponding curves for blood sugar in Figure 2 show the same general trend: recovery was complete $2\frac{1}{2}$ hours after adrenalin and a constant level was maintained in the control and the amphetamine experiments.

The possibility that other acids than lactic may have accumulated to a sufficient extent to modify acid-base balance was tested by measurement of CO_2 combining capacity of oxygenated blood at pCO_2 40. Notable decreases occurred following adrenalin but after $2\frac{1}{2}$ hours the original value was restored. The changes observed were approximately equivalent to the increases in lactate concentration, indicating that no other fixed acid was present in quantitatively significant amounts. There were no consistent changes in alkaline reserve following amphetamine injection.

The only other possibility that needs to be considered is that the drugs may have upset respiratory regulation enough to modify the pH and CO_2 content of arterial blood. Arterial blood was drawn from 2 subjects before and $2\frac{1}{2}$ hours after drug administration. There was an average decrease of about 1 vol. % after adrenalin and about 2 vol. % after amphetamine. If we assume that body fluids underwent a net loss of 1.5 vol. % of CO_2 during the $2\frac{1}{2}$ hours the total net loss was about 1 liter and the ratio of net loss to total production about 1 in 35. The R.Q., consequently, would be greater by about 0.02 than the R.Q. of the oxidative processes. It is by no means certain that changes in arterial blood reflect accurately changes in tissue fluids since their CO_2 content depends on the rate of blood flow and the oxygen utilization, as well as on composition of arterial blood. It is safe to say, however, that

2½ hours after injecting these drugs respiratory regulation was virtually normal in the case of adrenalin and only slightly affected in the case of amphetamine. In summary of the foregoing considerations, it appears that the R.Q. as measured over the entire period may have been slightly high in the case of amphetamine and was a fair measure of the proportion of carbohydrate utilized in the case of adrenalin.

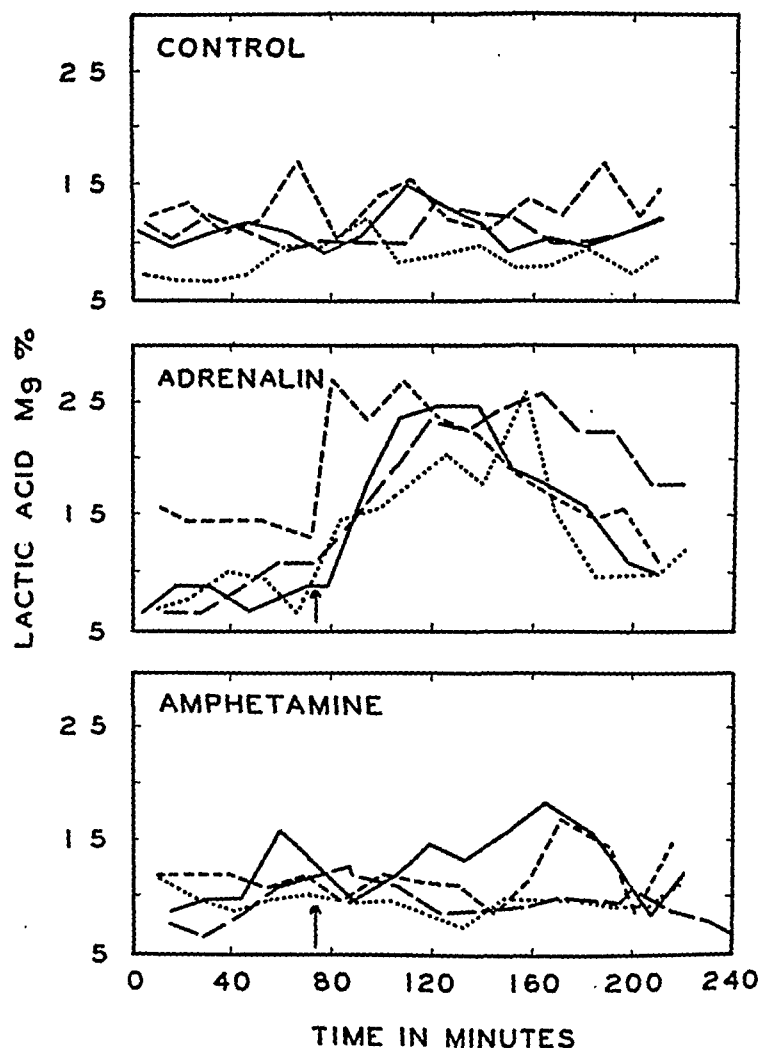


FIG. 1.—Blood lactate in control experiments and before and after intramuscular injection of 1 mg. of adrenalin or 20 mg. of amphetamine.

The R.Q. changes in the 4 individuals are shown in Figure 3. Only after adrenalin is there much deviation from the horizontal trend. The course is roughly parallel to the changes in lactic acid concentration. When lactic acid is accumulating, the R.Q. is higher than corresponds to oxidative processes, but if its rise is

solely dependent on displacement of CO_2 from reserves in tissue fluids there should be a correspondingly low level when lactic acid is being removed and CO_2 is being retained. An inspection of the curves does not indicate a drop in R.Q. values below the base line. With a single exception, the mean increments in R.Q. for each period after adrenalin for the 4 men are all positive; the mean

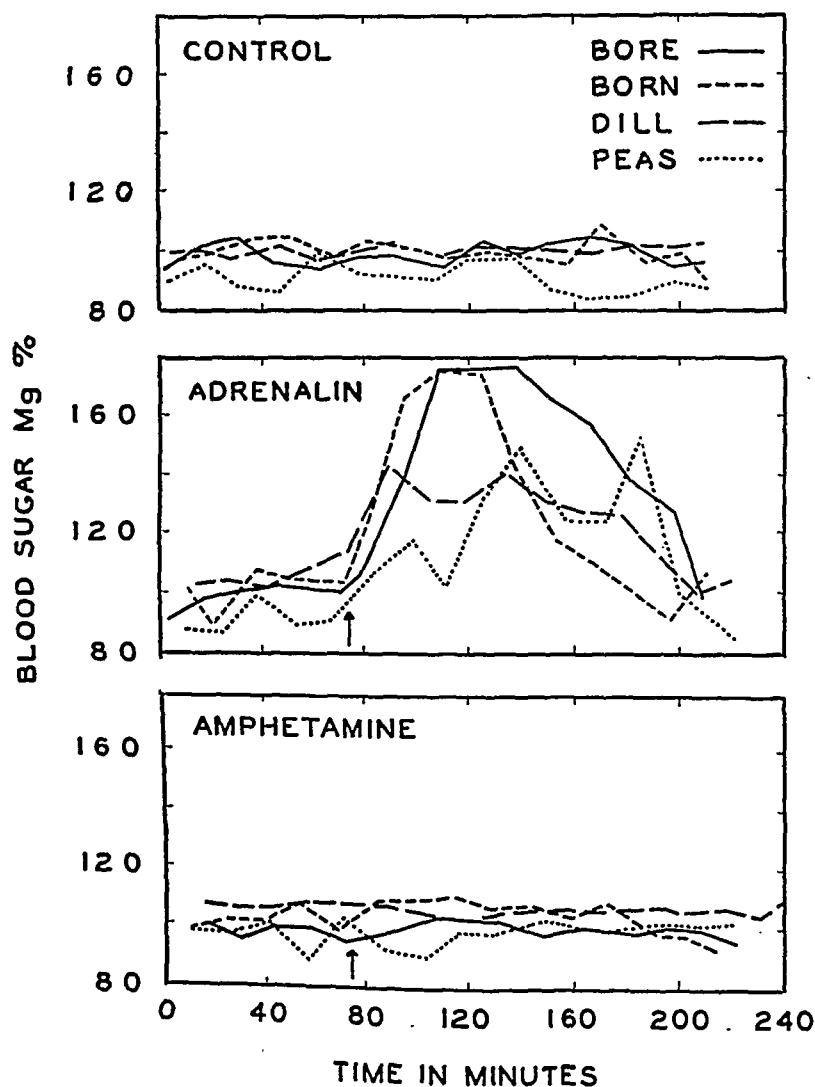


FIG. 2.—Blood sugar before and after adrenalin or amphetamine injection.

increment for the 40 postinjection periods is $+0.043$. It seems reasonable to conclude that the injection of adrenalin did not reduce utilization of carbohydrate in the body as a whole, but probably slightly increased it.

The appearance of acetone bodies in blood and urine is generally accepted as evidence of faulty utilization of carbohydrate. The report of Hubbard and Wright⁶ that acetone bodies in human blood

may increase from resting levels of from 0.2 to 0.7 mg. % up to 0.4 to 2 mg. % after injecting 1 mg. of adrenalin has been advanced as evidence that the adrenalin reduces utilization of carbohydrate.

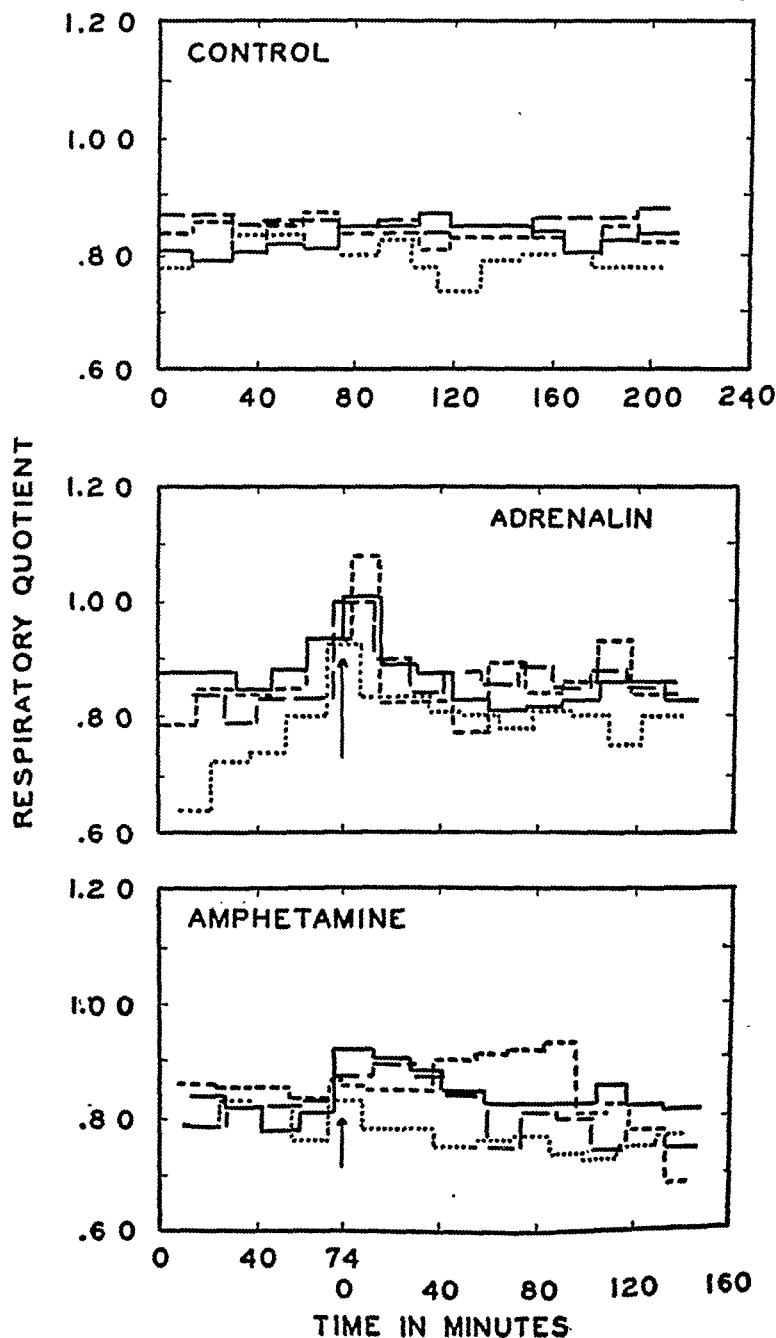


FIG. 3.—Respiratory quotient before and after adrenalin or amphetamine injection.

Determinations of total acetone bodies in blood and urine by Van-Slyke's method¹⁰ are summarized in Table 1. The changes after

adrenalin were like those observed by Hubbard and Wright and the return to the original level (or below it in 2 cases) also was noted. Acetone bodies increased in 3 of the 4 subjects after amphetamine. However, as great an increase occurred in the control experiments as after either drug. None of these changes are important quantitatively and we are not disposed to attach much significance to them. On the basis of the analyses of blood alone we are of the opinion that adrenalin was not responsible for an increase in acetone bodies and may have delayed the onset of ketosis that normally occurs 18 to 24 hours following the last meal. This suggestion is supported by the analyses of urine. All subjects exhibited a slight ketonuria in the control observations while none did so after adrenalin.

TABLE 1.—ACETONE BODIES.

(All concentrations are in mg. per 100 cc. Zero time corresponds to beginning of first metabolism period.)

Mean time of samples, minutes	Blood.				Urine acetone.	Urine vol., cc.
	66	96	125	213	220	220
Control:						
Borel	0.2	0.2	0.4	...	0.5	472
Bornstein	0.1	0.4	0.9	...	4.8	185
Dill	1.1	2.1	2.0	...	0.3	432
Pease	0.2	0.6	1.0	...	8.9	306
1 mg. adrenalin at 74 minutes:						
Borel	0.4	0.1	0.0	0.2	0.0	855
Bornstein	0.2	0.6	0.4	0.2	0.0	
Dill	0.2	0.6	0.2	0.2	0.0	460
Pease	0.5	1.0	0.7	0.2	0.0	
20 mg. amphetamine at 74 min.:						
Borel	0.2	0.4	0.7	0.9	0.0	
Bornstein	0.1	0.2	0.7	0.0	0.0	400
Dill	0.0	0.7	0.1	0.6	0.0	
Pease	0.7	0.2	0.0	0.7	6.0	292

Oxygen Consumption. The calorogenic effect of adrenalin is well established, but there have been conflicting reports regarding the oxygen consumption after amphetamine administration. The graphic records of our experiments in Figure 4 show quite clearly that there was a sharp increase in metabolic rate after adrenalin with a return to the level of control experiments after $2\frac{1}{2}$ hours, while after amphetamine the rise was less abrupt but more sustained. The mean increments in oxygen consumption in Periods 5 to 14 over the mean value for Periods 1 to 4 averaged 7.7 cc. per minute in the control experiments, 39 after adrenalin and 25.1 after amphetamine. The increments during the last $\frac{1}{2}$ hour were, in the same order, 12, 12 and 30. This is good evidence for the more sustained nature of the calorogenic influence of amphetamine. A quantitative measure of the calorogenic effect of these drugs must take into account the tendency of metabolism to rise in the control experiments, possibly because of restlessness. It was greater, on the average, by 3% during the last 10 periods than during the first

4 periods. Assuming that the same influences were operative during the drug experiments, we are left with an increase, during the $2\frac{1}{2}$ hours following injection, of 13% after adrenalin and 7% after amphetamine. It is possible that these increases in metabolic rate

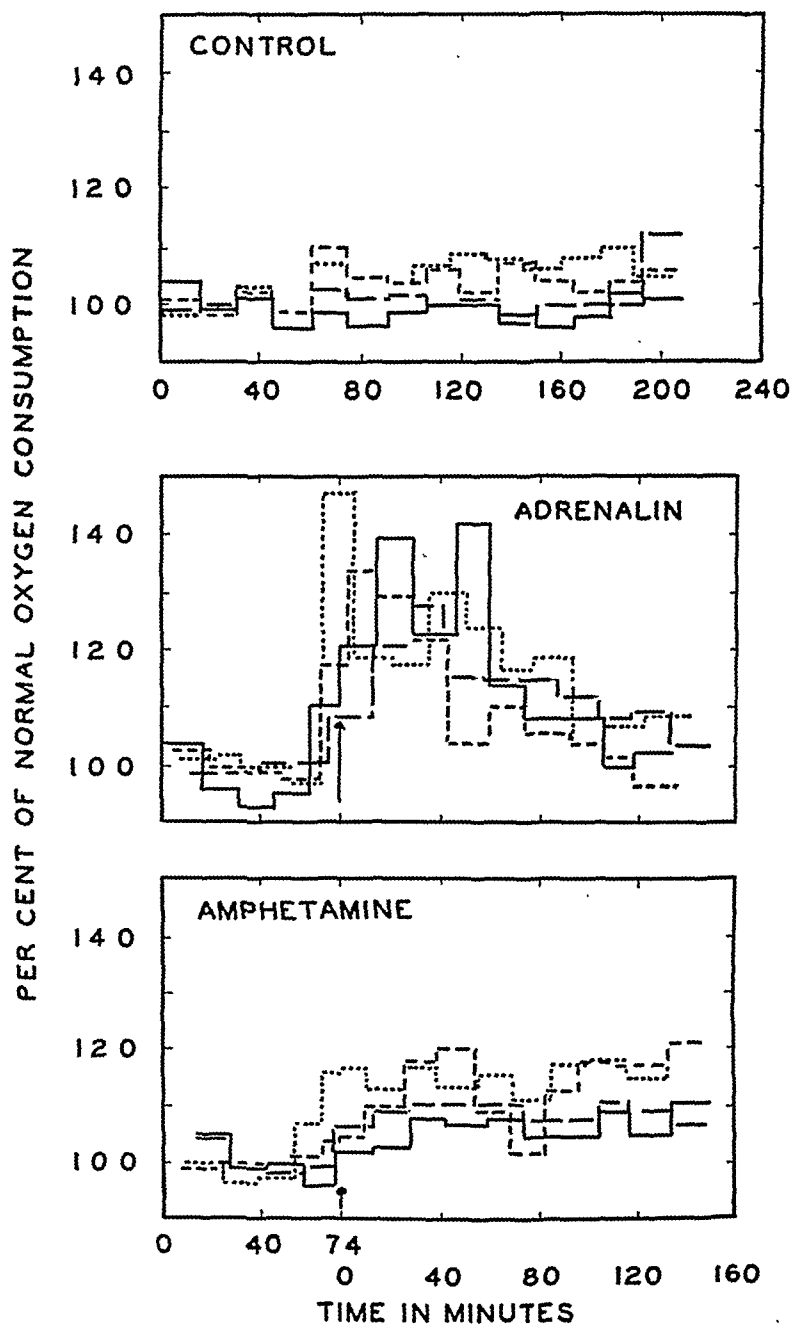


FIG. 4.—Effects of adrenalin and amphetamine injections on oxygen consumption. The normal value is taken as the mean oxygen consumption over a period of about 1 hour before administering the drug.

depend in part on greater restlessness rather than entirely on intrinsic calorigenesis but of this we have no measure.

Respiratory Regulation. The facts already presented regarding arterial blood have a direct bearing on respiratory regulation. There was the well-known tendency to overventilate while lactic acid concentration was rising after adrenalin, and when the original concentration was restored the CO_2 content of arterial blood closely approached its original level. At the same time the respiratory rate either increased slightly or remained constant. After amphetamine the respiratory rate remained constant, but there was a slight tendency to overventilate as shown by the lower concentration of CO_2 in arterial blood, already referred to, and a lower percentage of CO_2 in expired air.

Pulse and Blood Pressure. The transient effect of adrenalin on metabolism was accompanied by considerable increases in pulse rate (Fig. 5) and in systolic blood pressure, and by a significant decrease in diastolic blood pressure (Fig. 6). Amphetamine, on the other hand, produced little effect on pulse rate (in 1 man there was a decrease and in another an increase) but a large and sustained effect on systolic blood pressure. Just as the metabolism had reached its highest level in the last hour, so the systolic pressure tended to rise and in 2 subjects was highest at the end. The diastolic pressure also increased somewhat in 3 men and very considerably in the fourth. While both drugs raised the systolic blood pressure the mechanisms probably are different since the heart rate is increased in the 1 case and virtually unchanged in the other.

Discussion. Experiments such as ours have effects that depend on rate of absorption and rate of destruction of the drug. There is also the possibility of increased liberation of antagonistic substances—such as insulin. From the pharmacologic point of view, more easily interpretable results might be obtained by perfusion of isolated organs, but under many circumstances physiologic action can best be judged by observations of the intact and non-anesthetized animal. In interpreting our experiments we cannot deduce simple cause and effect relations, but it is possible to evaluate the resultant of the interplay of forces set in action by injection of these drugs.

The disagreement regarding the effects of adrenalin on utilization of carbohydrate is a consequence of inadequate data. In the early stages of the argument it was assumed that since blood sugar increased, utilization of carbohydrate increased. Later it was shown that the R.Q. increases but this was attributed to displacement of CO_2 by lactic acid. The antagonistic relation between adrenalin and insulin and the report of Hubbard and Wright⁶ that acetone bodies in the blood increase after adrenalin injection gave support to the opinion expressed by Peters and Van Slyke⁹ that adrenalin interferes with carbohydrate utilization. There is no basis for such

a conclusion in the work of Cori and Cori,² and our experiments in exercise⁴ demonstrating increased utilization of carbohydrate do not conflict with their observations. The present experiments on resting subjects in the postabsorptive state show a much smaller

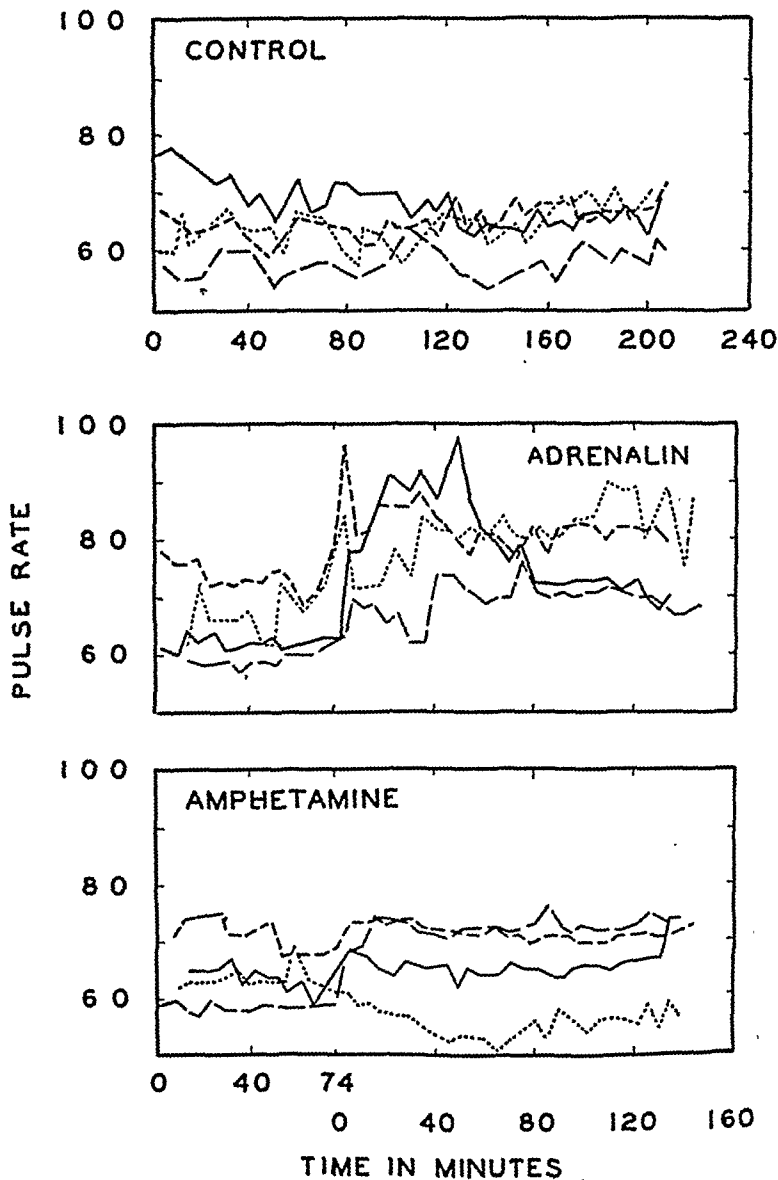


FIG. 5.—Pulse rate before and after adrenalin or amphetamine injection.

rise in R.Q. than in exercising subjects: this observation is in agreement with Cori's conclusion that the proportion of mobilized glycogen oxidized depends on the metabolic state of the organism. If our resting subjects had had smaller reserves of carbohydrate, there might have been no change or even a reduction in its oxidation,

as seen by Cori in rats that had fasted for 24 hours. This is suggested by the results of some preliminary experiments on subjects who had been 24 hours without food. Injection of adrenalin under

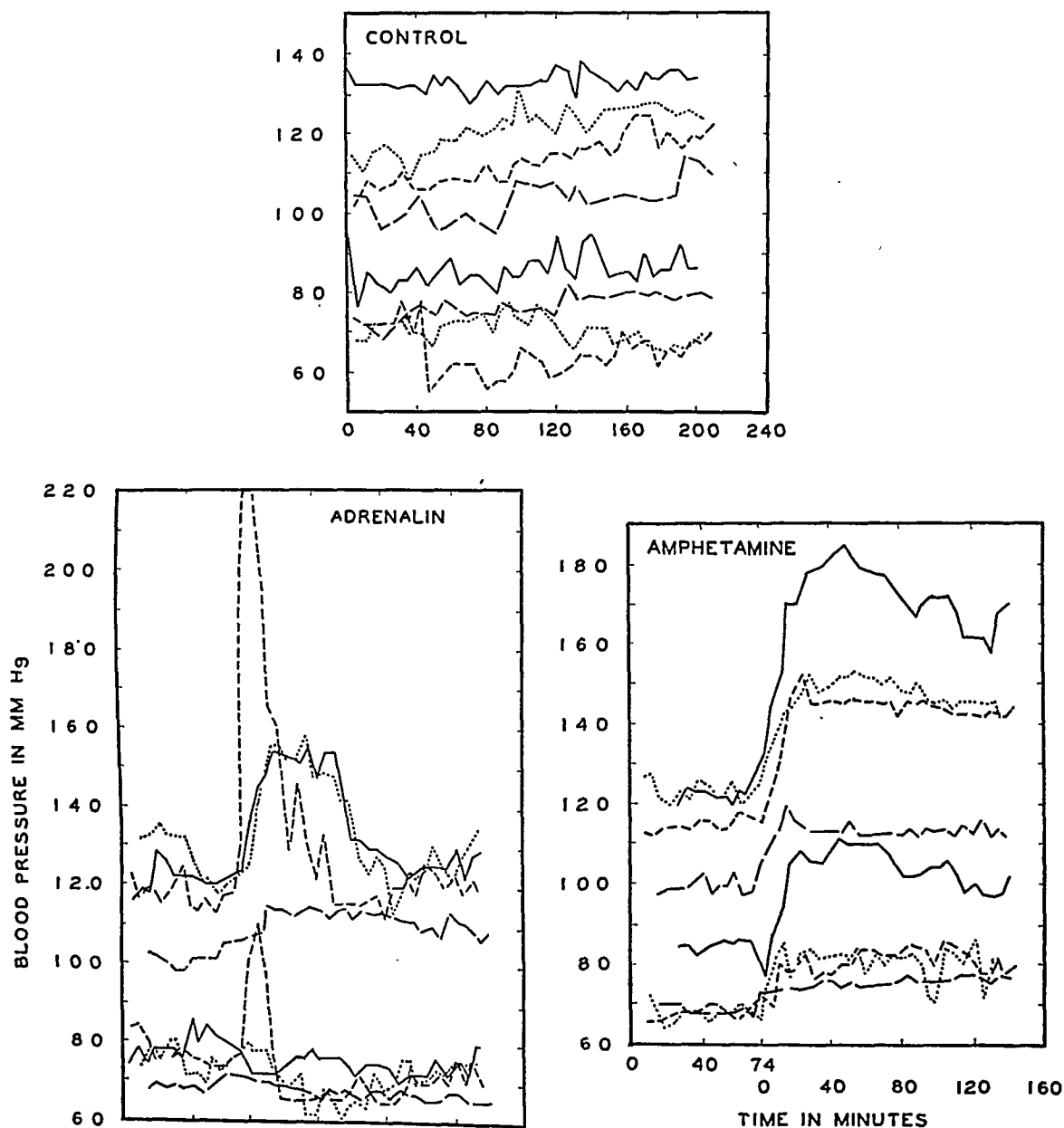


FIG. 6.—Systolic and diastolic blood pressure before and after adrenalin or amphetamine injections.

such circumstances produces an unmistakable rise in urinary acetone, in contrast with the experiments reported here on subjects who had been without food for from 12 to 16 hours.

We agree with the conclusion of Courtice, Douglas, and Priestley³ that in fasting subjects at rest there is little effect of adrenalin injections on the proportion of carbohydrate utilized. In 1 of their subjects, the mean R.Q. during 150 minutes following the subcutaneous injection of 0.5 mg. of adrenalin decreased 0.02 and in a second it was unchanged. We cannot accept their deduction from such experiments that adrenalin does not increase carbohydrate utilization in exercising subjects. In our opinion, the affirmative experimental evidence of Dill, Edwards, and de-Meio⁴ on this subject is conclusive.

The qualitative effects of adrenalin and amphetamine are no less interesting than the quantitative variation among normal individuals. According to preliminary observations the types of response seen, particularly in blood sugar and in blood pressure after adrenalin (Figs. 2 and 6), are apt to be characteristic of the individual. The significance of this phenomenon can only be determined by repeated observations on a number of subjects of different emotional types. There is the prospect of obtaining by such tests an objective index to the effectiveness of hormonal regulation and of the autonomic nervous system, at least in so far as carbohydrate metabolism and cardiovascular mechanisms are concerned.

Summary. Intramuscular injections of adrenalin in normal fasting men either did not change or slightly increased the proportion of carbohydrate utilized during the period in which blood sugar and lactate were elevated. Acetone bodies in blood and urine fluctuated within the normal range. Amphetamine did not modify carbohydrate utilization or the concentrations of sugar, lactate or acetone bodies in the blood. It had a calorogenic effect that was smaller in magnitude but more sustained than that of adrenalin. The rise in systolic blood pressure after amphetamine was greater in 1 subject, and in all subjects was more sustained than after adrenalin. In contrast with adrenalin, amphetamine produced a small but consistent rise in diastolic pressure.

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BOOK REVIEWS AND NOTICES

THE CLINICAL AND EXPERIMENTAL USE OF SULFANILAMIDE, SULFAPYRIDINE AND ALLIED COMPOUNDS. By PERRIN H. LONG, M.D., Associate Professor of Medicine, The School of Medicine, The Johns Hopkins University; Associate Physician, The Johns Hopkins Hospital, etc., and ELEANOR A. BLISS, Sc.D., Fellow in Medicine, The School of Medicine, The Johns Hopkins University. Pp. 319. New York: The Macmillan Company, 1939. Price, \$3.50.

In this monograph on sulfanilamide and sulfapyridine and allied compounds the authors have thoroughly reviewed the literature up to 1939. Laboratory workers will find complete bibliographies pertaining to the chemotherapy of experimental bacterial infections and experimental toxicity and comparative pharmacology of sulfanilamide and allied compounds. The section on the mode of action of sulfanilamide is well summarized on page 141, "So far, then, no theory has been evolved which adequately explains the mode of action of these sulfur benzene derivatives The speculations of Levaditi, Lockwood, and Mellon . . . should prove a stimulus to other workers."

Every practicing physician would profit by reading the chapters dealing with the clinical use and the clinical toxic manifestations of sulfanilamide. Unfortunately, at the time of writing, the authors had had little experience with sulfapyridine, and the 11 pages devoted to the clinical use of it serve only as an introduction to this new sulfanilamide derivative. Drs. Long and Bliss are to be commended on this accurate presentation of such a complex and ever-increasing phase of chemotherapy.

H. F.

MENSTRUAL DISORDERS. Pathology, Diagnosis and Treatment. By C. FREDERIC FLUHMANN, B.A., M.D., C. M., Associate Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco; Assistant Visiting Obstetrician and Gynecologist to Lane and Stanford University Hospitals, etc. Pp. 329; 119 illustrations. Philadelphia: W. B. Saunders Company, 1939. Price, \$5.00.

DR. FLUHMANN's clinical experience has been combined with the essence of his scientific research to produce a most welcome volume on the subject of "Menstrual Disorders." The subject matter is divided in logical sequence into 19 chapters which cover all the phases of the subject.

The first 5 chapters discuss the history, and physiologic and anatomic changes of the reproductive organs during the menstrual cycle, while a chapter on the comparative physiology of menstruation explains biologic differences in various mammals. Of particular value is a chapter on modern methods of investigation in which Dr. Fluhmann discusses the methods of analysis used to determine the content of the different hormonal elements in various body fluids. He also discusses and clarifies the significance of the results and the relative unit values of such tests. He is conservative in his statements as to therapeutic value of various hormones. In this connection he lists the commercial preparations now available, and also discusses the subject of irradiation of the ovaries and hypophysis. The latter part of the book takes up etiology, pathology, and treatment from a general standpoint, as well as by hormones. The book closes with an excel-

lent presentation of the modern conception of the menopause, and the methods of alleviating the often troublesome symptoms.

The author has been conservative in his suggestions for treatment in the various diseased conditions discussed, realizing, undoubtedly, the truth of his statement he makes in Chapter 8: "Most menstrual disorders are not primary diseases, but are secondary developments from systemic and pelvic condition." The book is highly recommended to the entire profession, for there are few physicians who do not come in contact with some expression of menstrual disorders in their daily practice. P. W.

PROBLEMS OF AGEING. Biological and Medical Aspects. A publication of the Josiah Macy Jr. Foundation. Edited by E. V. COWDRY, Washington University, St. Louis. Twenty-six Contributors. Pp. 758; 120 illustrations, many tables. Baltimore: The Williams & Wilkins Company, 1939. Price, \$10.00.

THIS book is composed of 25 chapters by as many different authors who cover a range in their respective fields broad enough to include botany, anthropology, geriatrics and in particular the ageing process as seen in each system of the body individually. The importance of the study from a broad human aspect is self evident. From the point of view of the medical profession in this day of diminishing childhood mortality, the consideration of this process and in particular the early changes indicative of age becomes the basis of the preventive medicine of the later decades. So sharp a focus as the title implies when dealt with by so many authors has of necessity led to some overlapping of the material. This has proved in the main an advantage, however, for the subject when it ceases to be purely descriptive becomes at once rather speculative and hence a contrast of points of view is advantageous. On the other hand, one is at times impressed with the possibility that an author is trying too carefully to stay within his field and thereby contracting an expression of opinion that would be better if expanded. For the practitioner of medicine the book holds a supply of factual tabulated data that is easily accessible and is as essential to a consideration of the ageing patient as standard tables of height and weight are for those dealing with children. W. A.

MOLDING AND CASTING. Its Technic and Application for Moulage Workers, Sculptors, Artists, Physicians, Dentists, Criminologists, Craftsmen, Pattern Makers and Architectural Modelers. By CARL DAME CLARKE, Associate Professor of Art as Applied to Medicine, University of Maryland School of Medicine. Pp. 308; 69 illustrations. Baltimore: The John D. Lucas Company, 1938. Price, \$4.50.

A MOST valuable working compend for those employing the plasters and waxes in impression and reproduction work. This book is of particular value for the many formulæ given and the details of technique. It is strongly recommended as an authoritative reference book. G. W.

OH, DOCTOR! MY FEET! By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 116; 3 illustrations and 6 plates. New York: D. Appleton-Century Company, 1939. Price, \$1.50.

THE author of that splendid work "The Human Foot" has tried to popularize foot care. This attempt suffers from a somewhat lumbering and weighty humor. G. W.

THE MARCH OF MEDICINE. Selected Addresses and Articles on Medical Topics, 1913-1937. By RAY LYMAN WILBUR, M.D., President of Stanford University. Pp. 280. Stanford University, Calif.: Stanford University Press, 1938. Price, \$2.75.

DURING his distinguished career as physician, teacher, administrator and cabinet officer, the author has had many calls to bring messages of counsel and inspiration, based on his rich and varied experience, to many groups, lay and medical. In this volume have been gathered thirty addresses, some reprinted from journals and society proceedings, some appearing in print for the first time, delivered over a span of 25 years. Dealing with various phases of medical teaching, postgraduate education, public health and medical economics, they give a remarkable survey of the progress and the problems of medicine and the medical profession that well merits the title, taken from that of the closing article, *The March of Medicine*. All physicians and medical students will find here much that interests and that challenges to thought and action. R. K.

SURGICAL APPLIED ANATOMY. By SIR FREDERICK TREVES, BART. Pp. 748; 192 illustrations (66 in color). Tenth edition, revised by LAMBERT ROGERS, M.Sc., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of Wales; Honorary Surgeon and Director of the Surgical Unit, Cardiff Royal Infirmary, etc. Revised from the ninth edition, prepared by the late PROFESSOR C. C. CHOYCE, C.M.G., C.B.E., M.D., F.R.C.S. Philadelphia: Lea & Febiger, 1939. Price, \$4.50.

This Applied Anatomy seems to require a new edition almost every year or so. The same format has been maintained as was present in the other editions. In this edition the sections on the eye, ear, nose and throat have been modernized and new sections and illustrations have been added throughout the book. It should still maintain its position as a readily accessible, anatomic reference manual and should appeal to students of anatomy and surgery because of its small size, its excellent subject material and its relatively low cost. L. F.

CANCER OF THE COLON AND RECTUM. Its Diagnosis and Treatment. By FRED W. RANKIN, B.A., M.A., M.D., Sc.D., F.A.C.S., Surgeon, St. Joseph's and Good Samaritan Hospitals, Lexington, Ky., and A. STEPHENS GRAHAM, M.D., M.S. (in Surgery), F.A.C.S., Surgeon, Stuart Circle Hospital, Richmond, Va.; Assistant Professor of Surgery, Medical College of Virginia. Pp. 358; 133 illustrations and 54 tables. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.50.

THE authors state that their purpose is to present the progress in the diagnosis and practical offensive maneuvers against cancer of the large bowel, one of the outstanding surgical accomplishments of the past quarter century. They offer not only their own experience, which has been wide, but also that of other authors.

The first section, general considerations, thoroughly discusses the anatomy and physiology of the large bowel, the incidence and etiology of its cancer and its pathology, symptoms and differential diagnosis. The section on anatomy and physiology includes frequent surgical considerations. The authors give their opinion that most of the lesions of the large bowel begin as adenomatous polyps, which are discussed in detail. They consider the various grades of tumor (Broders) and show illustrative microphotographs.

Part II, on diagnosis and treatment, discusses such subjects as operability and prognosis, choice of operation, radiotherapy, operative mortality and end-results, pre- and postoperative treatment. The authors support the view that a colostomy is necessary in most cancerous lesions of the colon and rectum, in order to perform a sufficiently radical operation. They do not condemn resection with primary anastomosis; but believe that the old dictum that "the smaller and the earlier the growth the better the chance of cure and the more extensive the operation should be" still holds good today. In this section are also described the various operations for cancer in the various portions of the large intestines, giving indications for their use.

In the chapter on radiotherapy of carcinoma of the rectum, which he regards as a "surgical disease," Dr. F. M. Hodges limits radiotherapy to the treatment of inoperable cases or cases in which operation is refused. He uses both external radiation and the implantation of radium seeds.

The chapter on operative mortality and end-results contains a review of the published statistics of practically all the large clinics. The statistics are hardly comparable because of differences in classification but nevertheless will be useful for those interested.

An excellent chapter on the authors' technique and pre- and postoperative treatment is especially valuable for the detailed description of the routine which they have successfully used.

The last part of the book, on operative treatment, describes and illustrates the various procedures in detail. The final section discusses palliative and various miscellaneous procedures of value in connection with the treatment of carcinoma; they mention colocolostomy, resection of the presacral nerves and so forth. The book is relatively small but so well written and so nicely condensed as to be thorough in every detail. It is one which can hardly be omitted from the library of a medical man or surgeon who is interested in lesions of the large intestines.

L. F.

MEDICINE IN THE OUTPATIENT DEPARTMENT. An Introductory Handbook. By WINTHROP WETHERBEE, JR., M.D., Junior Visiting Physician, Boston City Hospital. With a Foreword by GEORGE R. MINOT, M.D., S.D., F.R.C.P. (EDIN. and LOND.), F.A.C.P., Professor of Medicine, Harvard University; Director, Thorndyke Memorial Laboratory; Visiting Physician, Boston City Hospital. Pp. 111. New York: Paul B. Hoeber, Inc., 1938. Price, \$1.00.

SOME excellent advice for the guidance of the medical student's first clinical steps in the outpatient department; concise, to the point, and conveniently encompassed in a pocket-size booklet. As Dr. Minot says in his foreword, "Every paragraph might be expanded to a long chapter, but the value of the contribution lies in the clear, brief, and fundamental statements with which every medical student should not only be familiar, but which he should never neglect to utilize."

R. K.

A TEXTBOOK OF PHYSIOLOGY. By WILLIAM D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Pp. 714; 291 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.00.

THIS admirable text is now issued in its sixth edition. Much new material has been added so that it is thoroughly up to date. The illustrations are selected so as to be in harmony with the text. It is a book well adapted for use in the instruction of dental students.

B. McG.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago, etc. Pp. 691; 1 illustration. Philadelphia: J. B. Lippincott Company, 1939. Price, \$5.00.

THAT a fourth edition has appeared since the first in 1934 proves that the book has achieved its purpose as a "simple, crystallized, practical and workable method of prescribing diets" in health and disease. New material includes chapters on Addison's disease and chronic hyperinsulinism, also extensive revision of the section on vitamins, and others. R. K.

OPERATIVE ORTHOPAEDICS. By WILLIS C. CAMPBELL, M.D., Memphis, Tenn. Pp. 1154; 845 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$12.50.

THIS book is a most important addition to surgical literature and an efficient supplement to recent books on orthopedics. It describes in detail with accompanying illustrations the current bone and joint operative procedures. These are chronologically arranged according to Surgery of Joints, Bone, Muscles, Tendons, Nerves, Static Affections and Congenital Deformities. The subject of Joints, for example, deals separately with the surgical procedures used in acute infectious arthritis, low-grade affections of joints, arthrodesis, ankylosis and deformity, arthroplasty, traumatic lesions of joints and dislocations. There are over 200 pages devoted to Fracture Surgery, covering acute, malunited, delayed and ununited fractures. The introductory chapters greatly enhance the clear presentation of the material by describing the author's method of estimating joint motion, the present concept of bone physiology and pathology, surgical technique, orthopedic instruments and apparatus, and surgical approaches to bones and joints. J. N.

MEDICAL MICROBIOLOGY. By KENNETH L. BURDON, Ph.B., Sc.M., Ph.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University School of Medicine, New Orleans; Senior Visiting Pathologist, Charity Hospital of Louisiana at New Orleans, etc. Pp. 763; 120 illustrations. New York: The Macmillan Company, 1939. Price, \$4.50.

THE title "Medical Microbiology" is very appropriate, as the text includes fungi, mold-like higher bacteria, protozoa, rickettsiae, spirochetes and viruses in addition to the true bacteria. Although distinctly medical in emphasis, the book is concerned primarily with fundamentals so may well be used by students interested in the general aspects of microbiology.

The book is extensively indexed and each chapter prefaced with a topical outline. Although there is no bibliography at the end of each chapter, one section of the appendix has been devoted to general, well-selected references. Another section of the appendix is devoted to review questions for each chapter.

Part I (236 pages) is devoted to fundamentals of microbiology. Many drawings, diagrams and photographs are employed which are very instructive. The historical treatise of the various phases of microbiology are very well done. Part II (59 pages) is devoted to the laboratory study of microorganisms. This, together with appendices A, B and C, constitutes a short but good practical summary of laboratory procedures. Part III (116 pages) is devoted to the subject of infection and resistance. This is short and concise with stress placed on fundamentals. Part IV (227 pages) is devoted to the microbiology of important infectious diseases. Here the discussion is grouped according to the regions of the body, such as infections

of the skin, mouth and throat, respiratory tract, eye and ear, genito-urinary tract and the intestinal tract. There are also chapters on wound infections; diphtheria; pneumonia; typhoid and paratyphoid fevers, dysentery, cholera; tuberculosis; infections acquired from animals; important virus diseases; infections and protozoan infections.

The discourse is very clear and practical. Fundamentals are stressed throughout. It is indeed a textbook and not a reference work. The book is to be recommended. H. M.

THE ENDOCRINE GLANDS. By MAX A. GOLDZIEHER, M.D., Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Pp. 916; 271 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$10.00.

THIS book covers "the diseases of the endocrine glands and their treatment," with discussions of anatomy and physiology. References are given at the end of subdivisions of each chapter; those to foreign literature appear to predominate. It would seem that it might have been better to choose more wisely those references which are of special merit than to cover quantitatively such an immense range of work, much of which seems of little value, especially when the author states that he intends "to discuss only what we know as established facts and not what we think may be so even if it be a logical postulate to be verified by future observations."

The author is not a dispassionate critic, but sometimes accuses those whose views are not in accord with his own as governed by prejudice, or a "nihilistic viewpoint," and "shocking" dogmatism. The book is colored by the author's personal points of view, with many of which the present Reviewer disagrees. Examples of these are his emphatic statements that enlargement of the adrenal medulla with increased secretion is capable of causing, presumably frequently, chronic hypertension; his view that thyroid crisis is due to a sudden breakdown of adrenal cortical function; that there is antagonism between the thyroid and the posterior lobe of the pituitary; his inclusion among pituitary disorders, of the toxemia of pregnancy, angioneurotic edema, and what he speaks of as "pituitary retention syndrome"; his use, in addition to subcutaneous injection, of pituitary extract and adrenal cortical extract by oral administration, which he admits is "frowned upon by the spokesmen of 'organized medicine.'"

Case histories and many illustrations are of interest.

I. Z.

THE MASSACHUSETTS GENERAL HOSPITAL. Its Development, 1900-1935. By FREDERIC A. WASHBURN, M.D., Director Emeritus. Pp. 643; illustrated. Boston: Houghton Mifflin Company, 1939. Price, \$4.00.

ONE of the oldest and most distinguished of this country's hospitals, the Massachusetts General Hospital, has been as efficient in keeping its own history as in conducting its other activities. Its early history (1811-1851) was recorded by Nathaniel Bowditch, Secretary and Trustee; the period from 1851 to 1872 by the Rev. G. E. Ellis, Trustee; and the ensuing period to 1900 by Mrs. Grace Myers, Librarian. Its history in the twentieth century, the subject of the present volume, is covered by one who was Director during most of this period of great expansion. The author can thus speak at first hand of the developments of the hospital itself, of the laboratories, of the Phillips House for private patients, the Baker Memorial for people of moderate means, the special departments, the outpatient departments, the medical social service and many other activities that

reveal the magnitude and complexity of a great modern hospital. Thus the story is of interest and value, not only to those who want all the facts about their cherished institution, but also to those concerned with the history of American hospitals at a period of their most rapid expansion. The more formal story is lightened by an entertaining chapter of Recollections of Medical House Pupils, gathered by J. H. Means. Here most any ex-intern can relive his hospital days and most any reader can get instructive sidelights on the medical advances and hospital life of the period. Chapters on Administration, Case Records, Finance, and similar topics add further to the value of this excellent work. E. K.

OPUSCULA SELECTA NEERLANDICORUM DE ARTE MEDICA. Fasciculus Quintus-Decimus quem Curatores Miscellaneorum quæ Vocantur Nederlandsch Tijdschrift voor Geneeskunde Collegerunt et Ediderunt. Petri Camperi Itinera in Angliam, 1748-1785. Pp. 264; many text illustrations and 17 plates. Amstelodami: Sumptibus Societatis, 1939.

THIS fifteenth volume of a series which has been appearing irregularly since 1907 gives five of Camper's Travel Journals to Great Britain, in the original Dutch on the left-hand pages, and in English on the right-hand pages. It is embellished with a Preface and an Introduction by B. W. Th. Nuyens, 43 pages of biographic notes and 17 large plates. Other of Camper's writings have already appeared in Vols. 12 and 13 of this series. E. K.

PATHOGENIC MICROÖRGANISMS. A Practical Manual for Students, Physicians and Health Officers. By WILLIAM HALLOCK PARK, M.D., Late Professor of Bacteriology and Hygiene, New York University College of Medicine, and Director Emeritus of the Bureau of Laboratories of the Department of Health, New York City, and ANNA WESSELS WILLIAMS, M.D., Former Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 1056; 247 illustrations and 13 plates (some in color). Eleventh edition. Philadelphia: Lea & Febiger, 1939. Price, \$8.00.

THIS edition is still "Park and Williams" as the revision was completed shortly before Dr. Park's lamentable death. The clearness, conciseness and practicability, so characteristic of Dr. Park's style, is evident throughout. It is medical microbiology to date.

The portions of the book devoted to bacteriology and immunology are very good. Part I, the general principles and methods of bacteriology, includes a chapter of 35 pages on bacterial variation by Dr. Philip Hadley and also a chapter of 12 pages on bacterial metabolism by Dr. Kenneth C. Blanchard. These two subjects are of vital interest to everybody concerned with bacteriology and immunology, no matter what phase of the subject might be their interest. Chapters written by authorities on these subjects are an asset to any text. Part II, the techniques and methods of bacteriology, contains 99 pages of very practical and important material. Part VIII is devoted to applied bacteriology, which includes the bacteriologic examination of water, air, soil, milk and shellfish and the practical use of disinfectants. These latter two sections, Parts II and VIII, make a very practical manual. Part III, the principles of infection and immunity, contains 9 chapters or 159 pages which in addition to being a good discussion is elucidated with charts, diagrams and outlines. Part IV comprised of 333 pages devoted to pathogenic microörganisms includes descriptions of the spirochetes and rickettsiæ in addition to the customary bacteria.

There are 6 chapters of 86 pages in Part V devoted to viruses and virus diseases which were written by Dr. Morris Schaeffer and are a credit to any textbook. The section on pathogenic yeasts, molds and actinomycetes, Part VI, was written by Dr. Fred D. Weidman. It is 54 pages in length and is the best treatise on this subject appearing in any American textbook. The section on pathogenic protozoa, Part VII, is 6 chapters, 63 pages, in length and is very good. References are included at the end of each chapter. The book is well indexed, very well edited, well printed and bound and is to be highly recommended.

H. M.

MEDICAL CLIMATOLOGY. Climatic and Weather Influences in Health and Disease. By CLARENCE A. MILLS, PH.D., M.D., Professor of Experimental Medicine, University of Cincinnati. Pp. 296; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, \$4.50.

"The human habitat on earth is one of highly fluctuating characteristics. It at all times dominates man's energy level and general vitality, forever holding him down to a bare existence level in tropical lowlands, or driving him forward impetuously in stormy middle temperature regions. This drive fluctuates widely from day to day, season to season, and through the years and centuries. Especially does the medical profession need a thorough knowledge of these forces and their effects on human diseases and general health. Health itself assumes a much more dynamic force in some climates than in others, and with this comes a change in the general disease picture. Infectious diseases become less deadly, but there appear increasing signs of breakdown from overwork of the body machinery. The practice of medicine thus varies widely from climate to climate. In the response of people to this climatic drive, there will in every region be found people who fail to adapt, for whom a change of climate may offer the only hope for a normal existence. It becomes the physician's duty properly to advise these unfortunate individuals." These nearly verbatim quotations give the essence of the argument of this fascinating and highly important book. Every physician should read it: he will find here much that is helpful, instructive, interesting and provocative of speculation, thought and study.

R. K.

THE SURGERY OF PAIN. By RENÉ LERICHE, M.D. (LYON), LL.D. (GLASGOW), F.R.C.S. (ENG.) (Hon. Causa), etc., Professor of Clinical Surgery, University of Strasbourg. Translated and edited by ARCHIBALD YOUNG, B.Sc., M.B., C.M., F.R.F.P.S.G., F.A.C.S. (HON.), M.D. (STRASBOURG) (Hon. Causa), etc.; Regius Professor of Surgery, University of Glasgow; Visiting Surgeon, Western Infirmary, Glasgow. Pp. 512. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.50.

THE author of this work, a general surgeon, has devoted much of his life to the study of so-called intractable pain, investigated in both clinical and experimental fields. As a result, the author has contributed much to our knowledge of the derivation of pain and its treatment. His best known work is "The Diagnostic Value of the Abolition of Pain by Regional Novocainization" and the function of the sympathetic nervous system in the production of pain.

This comprehensive study of pain in relationship to surgical treatment discusses the general problem of pain and analyzes the various types in separate chapters. The pains considered are trigeminal and post-traumatic neuralgias, causalgia, pains caused by amputations, vasoconstriction, juvenile arteritis, angina pectoris, cutaneous cicatrices, visceral disorders and the

pains of inoperable or recurrent abdomino-pelvic malignant tumors. Each malady is reviewed thoroughly from the standpoint of cause, mechanism of pain production, rationale of treatment and the results of various forms of treatment. The book is interesting as it is written in lecture style, thus permitting the author to use open and frank discussion.

He gives both clinical and experimental data in support of his views and methods of treatment. Concerning these, several points bear comment. His interesting theory of the function of the sympathetic nervous system in the production of pain is not in agreement with that of leading physiologists. The evidence for his rejection of the accepted work of Head and Mackenzie on visceral sensory representation is not convincing. Complete section of the trigeminal nerve for trifacial neuralgia, as recommended by the author, is unwarranted when the pain does not involve the first division. On the other hand, alcoholic injections are admittedly temporary but quite satisfactory in the relief of trifacial neuralgia. In spite of these variances from accepted theories, the author's honest and critical analysis of each subject makes it a most valuable work for the clinician, investigator and surgeon.

R. G.

THE ART OF ANÆSTHESIA. By PALUEL J. FLAGG, M.D., Visiting Anæsthetist to Manhattan Eye and Ear Hospital; Consulting Anæsthetist to St. Vincent's Hospital, New York, and to Woman's, Sea View, Jamaica, Mt. Vernon, Flushing, Mary Immaculate and St. Mary's Hospitals, Far Rockaway, New York, etc. Pp. 491; 161 illustrations. Sixth edition revised. Philadelphia: J. B. Lippincott Company, 1939. Price, \$6.00.

THE first 400 pages of this edition are the same as in the fifth, except for some changes in illustrations and a few added notes. This part of the book deals with nearly all phases of anesthesia from the author's viewpoint up to 1932. There are 7 added chapters in which an attempt has been made to cover some of the newer developments in bringing the book up-to-date. These include chapters on the carbon-dioxide absorption technique and the new drug, cyclopropane, which are brief and conservative. The remaining chapters discuss new techniques, dental anesthesia and analgesia, intubation of the trachea, causes of deaths from anesthesia, and pneumatology. The author, who is one of the pioneers of the present era of modern anesthesia, has stressed the need for improvement in the personnel of anesthesia staffs in most hospitals. He maintains that this branch of medicine should be able not only to care for surgical anesthesia, but also gas therapy, resuscitation, respiratory difficulties, plus teaching and research.

I. T.

NEW BOOKS.

Journal of Criminal Psychopathology, Vol. 1, No. 1, July, 1939. Editor: V. C. BRANHAM, M.D. Editorial Staff: H. R. WEISS, A.M., J. J. BROOKS, A.M., C. D. OWENS, A.B., J. RUBIN, M.D., J. SCHUYLER, A.M., W. G. ROSE, Ph.B. Pp. 85; illustrated. New York: Woodbourne Institution for Defective Delinquents, New York State Department of Correction, 1939. Issued Quarterly, free of charge.

Primer of Allergy. A Guidebook for Those Who Must Find Their Way Through the Mazes of This Strange and Tantalizing State. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 140; illustrations by JOHN P. TILLERY. St. Louis: The C. V. Mosby Company, 1939. Price, \$1.50.

Maternal Care and Some Complications. The Principles of Antepartum, Intrapartum, and Postpartum Care and of the Management of Some Serious Complications. Approved by The American Committee on Maternal Welfare, Inc. Edited by F. L. ADAIR, M.D. Prepared by W. C. DANFORTH, M.D., G. W. KOSMAK, M.D., R. D. MUSSEY, M.D., R. L. DE NORMANDIE, M.D., F. L. ADAIR, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 194. Chicago: The University of Chicago Press, 1939. Price, \$1.50.

Proctology for the General Practitioner. By FREDERICK C. SMITH, M.D., M.Sc. (MED.), F.A.P.S., Proctologist to St. Luke's and Children's Hospital, Philadelphia; formerly Associate in Proctology, Graduate School of Medicine, University of Pennsylvania. Pp. 386; 141 illustrations and 3 color plates. Philadelphia: F. A. Davis Company, 1939. Price, \$4.50.

A Handbook of Elementary Psychobiology and Psychiatry. By EDWARD G. BILLINGS, B.S., M.D., M.D. Cum Laude (IND.), Assistant Professor of Psychiatry, University of Colorado School of Medicine; Director, The Psychiatric Liaison Department of the Colorado General and Psychopathic Hospitals, etc. Pp. 271. New York: The Macmillan Company, 1939. Price, \$2.00.

Opuscula Selecta Neerlandicorum de Arte Medica. Fasciculus Quintus-Decimus quem Curatores Miscellaneorum quæ Vocantur Nederlandsch Tijdschrift voor Geneeskunde Collegerunt et Ediderunt. Petri Camperi Itinera in Angliam, 1748-1785. Pp. 264; many text illustrations and 17 plates. Amstelodami: Sumptibus Societatis, 1939. (Review p. 719.)

The Papworth Village Settlement. Report of the Committee of Management and Medical Director for 1938. Presented at the Twenty-second Annual General Meeting of the Settlement, June 30, 1939. Pp. 65; illustrated. Cambridge: Papworth Hall, 1939.

Papworth Research Bulletin for 1938, Vol. 2, No. 1. The Sims-Woodhead Memorial Laboratory. Illustrated. Cambridge: Pendragon Press, 1939.

An Introduction to Medical Mycology. By GEORGE M. LEWIS, M.D., Associate, and Assistant Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University; Instructor in Medicine (Dermatology), Cornell University, etc., and MARY E. HOPPER, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 315; 71 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, \$5.50.

Recent Advances in Medical Science. A Study of their Social and Economic Implications. By SIR EDWARD MELLANBY, K.C.B., M.D., F.R.C.P., F.R.S., K.H.P., Secretary to the Medical Research Council. (The Rede Lecture Delivered before the University of Cambridge on April 28, 1939). Pp. 62. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, 75c.

A Text-book of Occupational Diseases of the Skin. By LOUIS SCHWARTZ, M.D., Medical Director, United States Public Health Service, in charge of Dermatoses Investigations, Washington, D. C.; Lecturer, Department of Dermatology and Syphilology, New York University, etc., and LOUIS TULIPAN, M.D., Clinical Professor of Dermatology and Syphilology, New York University College of Medicine; Consulting Dermatologist, Manhattan General Hospital, etc. Pp. 799; 116 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$10.00.

- A Topographic Atlas for X-ray Therapy.* By IRA I. KAPLAN, B.S., M.D., Director, Radiation Therapy Department, Bellevue Hospital; Director, Division of Cancer, Department of Hospitals, City of New York, etc., and SIDNEY RUBENFELD, B.S., M.D., Associate Visiting Radiation Therapist, Bellevue Hospital; Instructor in Surgery, New York University Medical College, etc. Pp. 120; 55 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, \$4.00.

NEW EDITIONS.

- A Synopsis of Regional Anatomy.* By T. B. JOHNSTON, M.D., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 462; 17 illustrations. Fourth Edition. Philadelphia: Lea & Febiger, 1939. Price, \$4.50.

- Principles of Chemistry.* An Introductory Textbook of Inorganic, Organic, and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. With Laboratory Experiments. By JOSEPH H. ROE, Ph.D., Professor of Biochemistry, School of Medicine, George Washington University; Formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Pp. 503; 53 illustrations and 4 plates. Fifth Edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

There are relatively few changes in this edition. In bringing it up to date the most marked changes were made in the chapters on Structure of Matter, Vitamins and Internal Secretions. In the latter two chapters some of the recent developments in respect to structural chemistry have been included. The discussion of fundamental organic chemistry has also been enlarged and throughout the book there is a more liberal use of figures and diagrams. Part II on laboratory experiments has remained practically unchanged except for the inclusion of a few questions on the various experiments. The structural formulas have been omitted from the appendix. J. J.

- Microbiology and Pathology.* By CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas; Consulting Pathologist, St. Louis Southwestern Railway Hospital, Texarkana, Arkansas, and Mother Frances Hospital, Tyler, Texas, etc. Pp. 755; 165 illustrations and 25 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.25.

- Pathogenic Microorganisms.* A Practical Manual for Students, Physicians and Health Officers. By WILLIAM HALLOCK PARK, M.D., Late Professor of Bacteriology and Hygiene, New York University College of Medicine, and Director Emeritus of the Bureau of Laboratories of the Department of Health, New York City, and ANNA WESSELS WILLIAMS, M.D., Former Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 1056; 247 illustrations and 13 plates (some in color). Eleventh Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$8.00. (Review, p. 719.)

- Asthma.* By FRANK COKE, F.R.C.S., with the Collaboration of HARRY COKE, M.R.C.S., L.R.C.P., Honorary Physician, Charterhouse Rheumatism Clinic. Pp. 266; 19 illustrations. Second Edition, fully revised and illustrated. Baltimore: The Williams & Wilkins Company, 1939 (A William Wood Book). Price, \$4.00.

- Experimental Pharmacology and Materia Medica.* By DENNIS E. JACKSON, Ph.D., M.D., F.I.C.A., Professor of Pharmacology, Materia Medica, and Therapeutics in the University of Cincinnati College of Medicine, etc. Pp. 906; 892 illustrations, including 55 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$10.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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THE MECHANISM OF INSULIN CONVULSIONS.*

STUDIES on the dehepatized animal by Mann³⁰ and by Mann and Magath^{31a} in 1921 proved that a certain amount of sugar in the blood is essential for life and that hypoglycemia is accompanied by a characteristic group of symptoms in which convulsions usually occur. They also showed that the injection of *d*-glucose restores the animal in a condition of hypoglycemia to normal and that if glucose is administered to a dehepatized animal in amounts sufficient to maintain the concentration of sugar in the blood at the normal level, the characteristic symptoms of hypoglycemia do not occur. Banting and co-workers² reported in 1922 that in rabbits convulsions occurred when the level of the blood sugar fell to 45 mg. per 100 cc. of blood. Later authors, however, demonstrated by further work that the decrease of blood sugar to a specific level is not the sole cause of the convulsions. Thus, for example, Macleod²⁹ found in 1924 that convulsions may occur with a blood sugar of 67 mg. per 100 cc. of blood. At the same time he demonstrated that the blood sugar may be as low as 37 mg. per 100 cc. of blood without the appearance of convulsions. The conclusion was therefore reached that there exists no definite relationship between the occurrence of hypoglycemic convulsions and the actual level of the blood sugar. Fletcher and Campbell,¹² von Noorden and Isaac,³⁵ and Redisch⁴¹ reported the occurrence of convulsions despite a considerably elevated blood sugar. Bornstein and Holm⁴ confirmed this observation both in humans and in rabbits. Clough, Allen and Root⁶ pointed out that in animal investigations convulsions may accompany a lowering of the blood sugar to only 66 mg. per 100 cc. of blood, whereas there may be no convulsions with a blood sugar tension of 30 mg. per 100 cc.

* Abridgment of section of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Experimental Surgery.

of blood. Péneau and Simonnet³⁸ and Putter⁴⁰ likewise confirmed the observation of lack of association between convulsions and the level of the blood sugar.

Delezenne, Hallion and Ledebt,⁹ Laqueur, Grevenstuk and de Jongh,²⁸ and Langecker and Stross,²⁷ investigating this problem, concerned themselves with the purity of the insulin preparations which were employed and learned that similar results were obtained with chemically pure extracts. Pollak³⁹ in 1924 expressed the opinion that the diminished tension of the blood *d*-glucose is not the direct and sole cause of the convulsions and that the immediate agent is either some substance which is mixed with the insulin or a toxic substance which is formed after the insulin has been injected into the animal body.

Many authors have attempted to find the cause in the nervous system. Thus, Noble and Macleod³⁴ formulated the hypothesis that after the injection of insulin some metabolic product is formed which exerts toxic effects on certain centers in the pons and medulla oblongata. Likewise Dickson and co-workers¹¹ wrote of the presence of similar products and considered the convulsive phenomena to be the result of irritation in the forebrain and midbrain. Houssay and co-workers²⁴ expressed the opinion that irritation of the labyrinth and vestibule calls forth the convulsions.

Kokubun²⁶ in 1927 formulated the hypothesis that the convulsions of so-called insulin hypoglycemia are dependent on the formation of degradation products of urea. The formation of these degradation products is in turn dependent on an acute disturbance of liver function which is reflected in an elevation of the ammonium nitrogen of the blood. Nagasawa,³³ working with rabbits, was, in fact, able to demonstrate an elevation of the ammonium nitrogen during insulin hypoglycemia but stated that it is impossible to explain the convulsions by this elevation alone.

There is still some question as to the anatomic origin of the convulsions of insulin hypoglycemia. Olmsted and Logan³⁶ in 1923 stated that decerebrate cats with the pituitary body left intact maintain a high blood sugar level which is not materially reduced by insulin, whereas typical insulin convulsions can be induced in decerebrate cats whose pituitary body has been removed. They further found that the blood sugar percentage in decapitate cats may be lowered by insulin and maintained below the convulsive level of normal cats without the development of convulsions. The conclusion was reached that the locus of action of insulin is on the bulbar centers, particularly the respiratory center. Kleitman and Magnus²⁵ concluded in 1924, on the basis of experiments on rabbits, that hypoglycemia leads in some way to an irritation of the medulla and to the convulsions. As far as I have been able to determine, there have appeared in the literature no reports of attempts to corroborate either of these pieces of work.

There is no unanimity of opinion regarding the existence of pathologic changes in the central nervous system resulting from hypoglycemia. But little information has been gleaned from experimental studies on animals. Rather characteristic cellular changes have been reported by Wohlwill,⁴⁷ Grayzel,¹⁴ and Stief and Tokay.⁴³ However, the experience of others, who employed rabbits, coincides more with that of Baker and Lufkin¹ and indicates that there is no characteristic patho-

logic picture. Baker and Lufkin, Terbrüggen,⁴⁴ and Bowen and Beck⁵ carried out careful histologic studies on cases of hypoglycemia and reported the finding of petechial hemorrhages throughout the central nervous system. Bodechtel³ and Wohlwill⁴⁷ have reported extensive zones of degeneration in the cortex of the cerebral hemispheres. The microscopic picture of these zones was similar to those seen by Gildea and Cobb¹³ as the results of anemia, by Spielmeyer⁴² as the result of carbon monoxide poisoning and by Courville⁷ in patients who had died after nitrous oxide anesthesia. The changes in the nerve cells were thus seen to be non-specific. Terplan⁴⁵ expressed a similar view after studying 3 cases in which the patients died as the result of insulin shock. In 1938 Moersch and Kernohan³² reviewed the neurology and neuropathology of hypoglycemia and reported in detail 2 cases in which the patients died of chronic hyperinsulinism. They were able to describe lesions of the cortex which were "not simply the result of coma but of a definite, although not specific, degeneration which occurred antemortem."

It seems altogether reasonable to assume that the neurologic phenomena of the hypoglycemic state are the result of some physicochemical change in the nervous system that is bound up in some manner with the metabolism of carbohydrates. Present indications are that changes in the oxygen tension are at the bottom of these neurologic manifestations. Olmsted and Logan³⁶ were the first to suggest that anoxemia is an important factor in the genesis of hypoglycemic convulsions: "It may possibly be that through the lowering of the blood sugar certain oxidative processes become depressed to such a degree that the brain cells, which are known to be especially susceptible to lack of oxygen, are affected in much the same manner as in asphyxia." They noted (1) the similarities between the convulsions of insulin hypoglycemia and those of asphyxia and (2) the "dark and venous character" of the arterial blood when the sugar content was very low. In later experiments Olmsted and Taylor³⁷ found a slight fall in oxygen saturation of the arterial blood of dogs following insulin convulsions.

It remained for Holmes,²² however, to point out that *d*-glucose is essential in the normal utilization of oxygen by brain tissue. He demonstrated that gray matter utilizes more oxygen than white matter or spinal nerves and emphasized that the increased oxygen uptake in the presence of *d*-glucose is dependent on the conversion of *d*-glucose to lactic acid. Moreover, Holmes and Holmes²³ found that the glycogen content of the rabbit brain is small and very variable. They therefore stated that "glycogen plays a comparatively unimportant (or obscure) part in the carbohydrate metabolism of the mammalian brain, and that the organ is dependent for lactic acid precursor directly upon glucose supplied to it by the blood." Himwich, Koskoff and Nahum²⁰ and Himwich and Nahum,^{19a,b} however, have shown that both lactic acid and *d*-glucose are absorbed by the brain from the blood in normal, phloridzinized and depancreatized dogs. The brain does not convert or store these foodstuffs as glycogen. In depancreatized animals the respiratory quotient of brain remains unity—indicating the utilization of lactic acid—in the absence of insulin necessary for *d*-glucose oxidation. Holmes and Holmes^{21,23} have shown that carbohydrate is oxidized by brain tissue but only after transformation to lactic acid.

Himwich¹⁸ has pointed out the significance of this capability of brain tissue in affording it a factor of safety "in two available sources of energy—glucose or lactic acid." Holmes and Holmes have demonstrated that insulin diminishes the oxygen uptake of cerebral cortex and this has been confirmed by Wortis.⁴⁸ Since a low blood sugar is reflected in a low lactic acid level in the brain, Wortis expressed the opinion that the convulsions resulting from hypoglycemia act as a protecting mechanism by adding lactic acid—a food utilized by the brain—to the circulating blood medium.

The lactic acid content of gray matter apparently does not bear a direct relationship to the lactic acid content of the blood. Holmes and Holmes found a greatly decreased lactic acid content of the brain following an injection of insulin, while Dameshek, Myerson and Stephenson⁸ and other investigators found no decrease in blood lactic acid during the hypoglycemic reaction. Furthermore, as early as 1923 Mann and Magath^{31b} demonstrated that in totally hepatectomized dogs neither racemic nor *d*-lactic acid is effective in preventing the development of hypoglycemic symptoms, whether it is administered intravenously or through a jejunal stoma. They cautioned their readers, however, that these findings do not exclude the possibility that lactic acid may enter the cell in some other form and be utilized intracellularly.

In 1935 Dameshek, Myerson and Stephenson⁸ attempted to study the mechanism of the neurologic symptoms of insulin hypoglycemia in man, chiefly by comparing the content of *d*-glucose and oxygen in the vessels supplying the brain and the arm before and after the intravenous administration of insulin. They made the following observations by comparing the results of analysis of samples of blood withdrawn as nearly simultaneously as possible from the brachial artery, the internal jugular vein and the basilic vein: (1) The uptake of *d*-glucose by the brain became materially reduced during the severe hypoglycemic reaction, although that of the arm usually became increased. (2) The uptake of oxygen by the brain varied indirectly with the severity of the insulin reaction, becoming much reduced during the most severe reactions. (3) The blood lactic acid became increased during the reaction, no differences between vessels being noted. They concluded that the marked diminution in the arteriovenous difference in content of oxygen during the severe insulin reaction may signify actual diminution in oxygen uptake by the brain; if this is true, the neurologic symptoms of the insulin reaction may be due to the effects of a lack of oxygen on the brain.

Employing the technique developed by J. F. Heymans and Kochmann¹⁶ and DeSomer and J. F. Heymans¹⁰ for perfusion of the isolated head of the dog, C. Heymans, Jourdan and Nowak¹⁷ investigated the survival and revival of nerve centers following acute anemia. When the circulation of the perfused isolated head was interrupted, the palpebral, pupillary and motor reflexes disappeared after 3 to 4 minutes of acute anemia. The respiratory, cardioregulatory and vasomotor centers were at first excited but, after 4 to 5 minutes of arrest of circulation, they became paralyzed. The encephalobulbar centers, as well as the isolated head as a whole, were then apparently dead. The revival of the various nerve centers was investigated by reestablishing the cir-

ulation to the isolated head after periods of arrest of varying lengths. The observations were summarized as follows:

1. After an arrest of the circulation of 15 to 20 minutes, the palpebral and pupillary centers were definitely paralyzed, although the vasomotor and respiratory centers could be revived without difficulty.

2. When circulation to the isolated head was reestablished after an arrest of 30 minutes' duration, the respiratory, cardioregulatory and vasomotor centers could be revived and could resume their activity. The respiratory center, formerly considered the most sensitive to anemia, could be revived and could resume its activity even after 60 minutes of apparent death.

In 1935 C. Heymans and Bouckaert⁴⁵ studied the revival of the various nerve centers in the intact dog by reviving dogs after varying periods of apparent death from asphyxia. Their experiments demonstrated that in the intact animal also the respiratory, cardioregulatory and vasomotor centers can be revived after arrest of circulation for 30 minutes. When the arrest of circulation was limited to 5 minutes or less, there was generally complete recovery of the functions of all the centers. However, when the circulation was interrupted for longer periods the revived dogs exhibited narcosis, coma, rigidity and hyperthermia, symptoms probably indicative of lesions in the cerebral cortex and hypothalamus. These regions are apparently much less resistant to anoxemia than the medullary centers. Comparable results have been reported by Winkelbauer.⁴⁶

In conclusion, it may be stated that the signs and symptoms of insulin hypoglycemia are for the most part due to anoxia of the brain. Despite the fact that the center for hypoglycemic convulsions has been variously placed in the forebrain, midbrain, pons, medulla oblongata, labyrinth and vestibule, it seems much more logical to assume that the convulsions are due to abnormal impulses arising in the motor cortex. The convulsions are practically identical with those seen in idiopathic epilepsy and there is at present entire agreement that the convulsions of idiopathic epilepsy arise in the motor cortex. In hypoglycemia the explosions of abnormal nerve impulses are in all probability the expression of deficient utilization of oxygen by the cortical cells in the presence of a low blood sugar. Future advances in the medical therapy of hypoglycemia will no doubt come with the discovery of methods whereby the utilization of oxygen by the brain may be improved. At the present time, the only therapeutic means of obtaining this improvement is the injection of *d*-glucose.

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RADIOLOGY.

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ROENTGEN THERAPY OF INFLAMMATORY CONDITIONS.

IN 1896, shortly after the discovery of Roentgen rays by Wilhelm Conrad Röntgen, a number of physicians became interested in this new light as a diagnostic agent. It soon became apparent that the radiation was capable of evoking a cutaneous reaction consisting of erythema, dermatitis and even ulceration. This biologic effect attracted the attention of several observers who suggested that the newly discovered rays might have therapeutic value. The action of Roentgen rays (or radium) on different kinds of tissue was investigated experimentally and from these investigations considerable knowledge was acquired concerning the cellular effects of exposure to the rays. The therapeutic value of the rays was tested first in connection with inflammation of the skin, tuberculous processes such as tuberculous adenitis and cancer of the

skin or of deeper structures. Encouraged by the favorable action of the rays in various types of pathologic conditions, their therapeutic effect on other conditions was gradually put to the test. It was found that an increasing number of inflammatory conditions often responded favorably to suitable irradiation.

Desjardins² credited Williams with including, as early as 1902, among the pathologic conditions found to respond favorably to Roentgen irradiation: herpes zoster, psoriasis, eczema, acne vulgaris and rosacea, prurigo, lichen planus, lupus vulgaris or erythematosus and tuberculous adenitis or peritonitis. Some of these conditions were treated with more or less success from 1 to 5 years earlier by different physicians, including Freund (1897), Albers-Schönberg (1897), Gautier (1897), Rudis-Jicinsky (1898), Pusey (1900), and several others. In the preface to Belot's important book, "Roentgen Therapy for Cutaneous Diseases" (1904), Brocq asserted that "roentgen therapy already dominates the treatment of skin diseases." Belot added as amenable to Roentgen therapy sycosis, blepharitis, rhinophyma and mycosis fungoides.

During the next 15 years, the treatment of many other forms of inflammation was investigated. Many radiologists, even today, are not yet aware of these early investigations and reports, some of which are notable examples of painstaking work and keen observation.

Between 1904 and 1910, the main factors which govern the action of Roentgen rays on cells were discovered. It was during this same period that, as far as the therapeutic effect of Roentgen rays on many varieties of inflammation is concerned, that small or moderate doses were found sufficient and usually were superior to large doses, such as those employed in the treatment of most malignant processes. This was especially true of acute inflammations, in which a single exposure to a small dose (10 to 50 % of the erythema dose) often proved sufficient to arrest the pathologic process. In cases of chronic inflammation, larger but moderate doses (50 to 80 % of the erythema dose) had to be given and the dosage repeated at intervals for some time to cure the lesions or to obtain maximal improvement.

To pathologists it has been long known that one of the prominent features of many forms of inflammation, and especially of acute inflammation, is leukocytic infiltration, the degree of which varies according to the species of bacteria responsible for the inflammation, and perhaps also according to the number of bacteria present. In other words, the degree of leukocytic infiltration varies with the virulence of the infecting microorganisms. In a large proportion of cases in which the inflammation is caused by pyogenic bacteria, notably by staphylococci (furuncle, carbuncle, abscess, acute adenitis), the favorable effect of proper irradiation can be observed within 2 to 24 hours and this effect continues to increase thereafter. If the lesion was irradiated during the early part of its course, the pain subsided and disappeared, although the pain might increase for an hour or 2 before it commenced to diminish. The swelling abated and the lesion gradually resolved. When the lesion was not irradiated until later in its course, the resolving effect of the rays was less striking; pain diminished just as in the case of lesions which were treated earlier, but the analgesic effect took place more slowly. When the lesion was irradiated after suppuration had started, the suppurative process was hastened and it was necessary to provide

drainage sooner than would be the case with similar lesions which were not exposed to Roentgen rays.

These changes described were observed in about 75% of the lesions treated. When the inflammatory process was due to infection by streptococci, exposure to Roentgen rays was not followed by any modification which could be recognized as an effect of the rays.

Numerous experiments on animals have established the fact that lymphocytes in lymph nodes, spleen, circulating blood, intestinal follicles, thymus gland and other structures in which lymphoid cells are to be found are the most radiosensitive of all the different kinds of cells in the body. The neutrophils and the eosinophils are less sensitive than the lymphocytes, but only slightly so. Mucus-secreting epithelial cells (found chiefly in the salivary glands, stomach and intestine, and bronchi) are slightly less sensitive than the neutrophils and eosinophils, but they seldom play an essential or important part in inflammatory lesions.

When structures made up largely of lymphocytes are exposed to a small or moderate dose of Roentgen rays (or radium), a certain proportion of these cells subsequently undergoes degenerative changes and many are destroyed; the proportion of lymphocytes thus influenced depends on the dose of Roentgen rays. Warthin's experiments showed that this action of the rays began during irradiation and could be perceived microscopically within $\frac{1}{2}$ hour after exposure; in other words, as soon as sections of the irradiated lymphoid structures could be prepared and examined. A small proportion of lymphocytes remained unaffected and served as a nucleus for subsequent regeneration of these cells, unless excessive or repeated irradiation had destroyed them all. Beginning during irradiation and perceptible soon thereafter, the cycle of cellular changes, as they affected the lymphocytes, increased for 2 to 3 days; then the metabolic activity of the remaining cells continued at an abnormally low level, especially in relation to mitosis, for 1 to 3 or more weeks. After this, the remaining lymphocytes gradually recovered their ability to multiply and, after a time, partial or complete regeneration of these cells took place. When lymphoid structures were irradiated repeatedly, at relatively short intervals, an increasing proportion of cells were affected, fewer cells were able to survive, and their ability to regenerate and to replace the destroyed cells diminished more and more or the cells disappeared completely.

Degenerative changes induced by irradiation in the neutrophils and eosinophils in the circulating blood did not become perceptible until 12 to 24 hours after exposure. A smaller proportion of cells was affected by a like dose, and the resulting cellular changes were similar to those observed in the lymphocytes, although regeneration took place at about the same time and rate as that of the lymphocytes.

When the affected cells disintegrated, a subsidiary step was that adjacent reticular cells in the lymphoid structures or in other tissues in the irradiated area assumed the rôle of phagocytes and ingested the destroyed leukocytes. These reticular macrophages played an important part in disposing of bacteria and other noxious materials.

In lymphoid structures, the lymphocytes destroyed by the rays were replaced by connective tissue, but the proliferation of these cells was slow and did not become apparent until much later. In the meantime, the rapid regeneration of lymphocytes repopulated the lymphoid fol-

licles and tended to mask the increase in connective tissue. It was only after repeated irradiation had brought about marked or permanent disappearance of the lymphocytes that the increase in connective tissue became evident. Lymphocytes, neutrophils and eosinophils, destroyed while circulating in the blood, are not replaced by connective tissue; their contents (antibodies, ferments and so forth) are liberated in the blood stream and exert their effects in the same or in some other region.

Destruction of leukocytes is a prominent, if not the outstanding, effect of exposure to the rays. When, in acute inflammation, some of the infiltrating lymphocytes, neutrophils and eosinophils are destroyed by the rays, the contents of these destroyed cells, including the antibodies and other protective substances which have already formed, inevitably must be liberated and scattered among the remaining intact cells. Under these circumstances, it seems probable that the protective substances may become even more effective than when they were held within the cells before irradiation. There is little ground for the assumption that irradiation increases the production of antibodies. On the contrary, experimental investigation has shown that irradiation tends to diminish the formation of antibodies.

A satisfactory explanation of the influence of Roentgen rays or radium on chronic inflammation must be based on the pathologic character of the lesions and on the known action of the rays (as disclosed by experiments) on the kinds of cells present in the lesions. Proliferation of connective tissue is a more prominent feature than leukocytic infiltration. Chronic inflammatory lesions are characterized by varying degrees of central necrosis, caseous degeneration, calcification, or hyaline or amyloid changes; where any of these changes have occurred, the tissues are impervious to the action of the rays. The varying relative proportion of leukocytic infiltration and proliferation of connective tissue in any given lesion will therefore govern the response of the lesion to Roentgen therapy. For chronic inflammatory lesions, larger quantitative doses of rays are necessary and treatment must be repeated at intervals for some time if satisfactory results are to be obtained.

For acute inflammation, especially that due to infection by staphylococci or due to trauma, a single, small dose (from 10 to 50% of the erythema dose) is usually efficient and yields the best results. Occasionally, when a single exposure has not had the desired effect, a second exposure several days after the first may be indicated. The more acute the inflammation, the smaller the dose usually required.

It is important that the field of irradiation should not be confined too closely to the visible limits of the inflamed tissue, but should include a wide zone of apparently normal tissues. This is especially true when the inflammation is due to infection by virulent bacteria, such as streptococci or *Clostridium welchii*; in such instances, the advantage of having the rays act on leukocytes in the blood circulating through the inflamed region and all around it is of paramount importance. In treating these inflammatory lesions caused by highly virulent bacteria, good results have been obtained by using small doses and repeating them daily or twice daily over a period of several days. Roentgen rays generated at moderate voltage, such as from 100 to 150 kv. and filtered through 4 or 6 mm. of aluminum or through copper of equivalent filtration value,

are more effective than rays generated at 200 kv. or more. For chronic inflammation, generally, treatment must not be discontinued too soon. Even after the lesions and symptoms have disappeared, or have ceased to be active, it is wise to give the patient 1 or 2 additional treatments. The more chronic the lesion, the more essential is this precaution.

Hodges and Snead⁴ stressed (1) the value of the roentgenogram for disclosing unsuspected infections of sinuses and (2) the definite therapeutic value of irradiation for some types of sinus infection. Reviewing the literature on the experimental work done on this subject they arrived at the following summary of the effect of irradiation on infected membranes of the sinuses: "The effect of the x-ray treatment appears to be due primarily to an early destruction of the lymphocytes in the infected membranes. From 48 to 72 hours after treatment . . . there appears to be an increase in the number of macrophages. . . . These macrophages are seen to be laden with cellular debris and dead pigments. It is possible they also engulf bacteria. The membrane becomes gradually reduced in thickness but retains numerous plasma cells, polymorphs, and some histiocytes. After a week or more some fibrosis appears. There is no evidence of injury to the cilia, epithelium, or cellular elements other than the lymphocytes as the result of x-ray dosage."

Hodges and Snead obtained their best results in cases classified clinically as subacute or subchronic, in which symptoms were present for a period varying from several months to several years. Many of these patients have a cough and give a history of recurring colds and on roentgenologic examination of the thorax, exaggeration of the bronchovascular markings of the lower lobes is found. Roentgenologic examination of the sinuses discloses cloudy ethmoids with marked thickening of the membrane in the antra. They obtained good results with irradiation in the majority of cases in which symptoms were present for several years, usually with hyperplastic sinusitis and roentgenographic findings of marked cloudiness of the ethmoids and much thickening of the membranes in the antra. In these two groups of cases when roentgenographic examination disclosed an increase in the bronchovascular markings, small doses of irradiation were applied over the lungs with definite benefit.

In the group of cases in which early or reasonably early polypoid changes were found, especially in the nose, with a history of infection for many years, marked relief followed irradiation in the majority of cases. A number had return of the sense of smell and 2 had much improvement in vision following treatment. Others who were unable to breathe through the nose were relieved in this respect. Some who required repeated operations for removal of polypoid material had no recurrence of polypoid hyperplasia. Usually, the longer the duration of the infection or the more chronic and widespread the polyp formation, the poorer were the results from irradiation.

In the experience of Hodges and Snead, coöperation of the rhinologist and radiologist in the diagnosis, and follow-up of the results of treatment were essential for best results.

In the cases characterized by infection, 130 kv. with 6 mm. of aluminum filtration, about 300 r measured in air, was given in 3 or 4 treatments over a period of from 1 to 3 weeks. In those cases characterized

by polypoid hyperplasia, 200 kv. with 0.5 to 2 mm. of copper filtration, 600 r measured in air, was used.

It is an accepted fact that bronchiectasis frequently is associated with infection of the accessory sinuses of the nose. Hodges and Snead mentioned the benefit obtained from irradiation of the lung when accentuation of the bronchovascular markings was evident. Berek and Harris¹ reported the successful use of irradiation in the treatment of chronic suppurative bronchiectasis. In an analysis of the factors concerned in the results obtained, after a review of the experimental work on animals and a correlation of the experimental results with those obtained by irradiation among human subjects, these authors concluded that the effect was owing to possible enhancement of immunizing processes both through the action of the rays in stimulating antibody action and the physicochemical alterations of the local tissue reactions rather than to diminution or abolition of secretion. They thought it most logical to assume that the results obtained were due to the action of the Roentgen rays on chronic inflammatory processes.

Roentgen therapy was instituted in a series of cases of chronic suppurative bronchiectasis. All patients subjected to treatment had been observed previously over a period of several months at least, and were known to have a chronic lesion with sustained high level of expectoration without marked spontaneous remissions. All these patients were investigated thoroughly by means of bronchography and bronchoscopy and the diagnosis of chronic suppurative bronchiectasis was clearly established. The majority of the patients were variously and unsuccessfully treated by bronchoscopic drainage and lavage, pneumothorax, phrenic nerve interruption, and climatotherapy. Roentgen therapy was given as a last resort. The alternative for these patients was radical operative intervention, such as lobectomy or pneumonectomy.

To control observations on the effect of the treatment, no other form of therapy was used coincidentally. The patients were ambulatory, for the most part, during treatment. Roentgen therapy was given over a period of approximately 3 months, cross-firing all the diseased and secreting lobes (as revealed by bronchography and bronchoscopy) through anterior, lateral and posterior fields, utilizing 3 portals for one lobe or 5 for the hemithorax, as necessary. The physical factors were: 180 to 200 kv.; 0.5 mm. copper plus 1 mm. aluminum filtration; the focal skin distance was 50 cm. Each treatment consisted of 75 r, measured in air, to two or three fields. The patients usually were treated 2 to 3 times a week; the average total dose used was approximately 1500 r through each port of entry. At least 4 months was allowed to elapse after irradiation to secure the full measure of improvement. If the lungs were involved bilaterally, the authors found it of advantage to treat both sides simultaneously.

Patients who previous to treatment had experienced hemoptysis and episodes of pneumonitis were free of such attacks and episodes subsequent to treatment. A large proportion of all patients was relieved of cough and expectoration. Clubbing of the digits subsided surprisingly in a number of cases. Improvement was sustained during all the follow-up examinations, in some cases over a period of 6 years. During this period, infections in the upper part of the respiratory tree were experienced repeatedly by their patients, characterized by slight

increase in expectoration but this was without odor, and there was no recurrence of harassing cough and no profuse, foul expectoration. In several of the most severe cases, great improvement was experienced and this has been sustained without recurrence for more than 6 years. The symptomatic improvement in the majority of cases has been striking.

During the course of treatment, the patient's symptoms may be exaggerated, which may lead to discouragement on the part of the patient and also on the part of the therapist. This is a definite part of the effect of radiation encountered in the treatment of this disease.

Powell⁵ reported the use of Roentgen therapy in 105 cases of lobar pneumonia and in 30 cases of bronchopneumonia. As soon as the diagnosis was made on the basis of the history, the physical examination, the condition of the blood and the roentgenologic examination, treatment was commenced. A definite leukopenia such as is found associated with some postinfluenzal pneumonias was the only contraindication to Roentgen treatment in his experience. Treatment was given anteriorly or posteriorly over an area a little larger than that represented by the involved portion of the lung. Using 135 kv. with 3 mm. of aluminum filtration and a target skin distance of 40 cm., a dose of 250 to 350 r was given. If the temperature had not returned to normal or to below normal within 36 hours after the first Roentgen treatment, a second treatment of 200 r was given over the opposite cutaneous area. When Roentgen treatment was given before consolidation was complete, consolidation might spread, but the patient would show the usual clinical improvement, and the temperature, pulse, respiration and number of leukocytes would return to normal. A few cases with mixed infection required a third or fourth treatment, using, of course, successively smaller doses so as to avoid a cutaneous reaction. Bronchopneumonia seemed more variable in its response to radiation therapy, but Powell was of the opinion that Roentgen therapy materially reduced the mortality rate of this condition.

Patients were treated in all stages of the disease, from the first day to, in 1 case, the eleventh day. Most of the patients were relieved of distress and experienced general symptomatic improvement within a few hours, and in more than one-third of these cases the temperature decreased to normal within 36 hours after treatment.

Dowdy, Heatly and Pierce³ used radiotherapy as an adjunct in the treatment of acute otitis media in a series of 30 cases, with encouraging results. The character of the discharge either remained thin or became thin after irradiation. This resulted in adequate drainage of the middle ear cavity. With the reduction of congestion, the Eustachian tube tended to be more completely patent, thus adding to the patient's comfort. Occasionally, drainage from the middle ear was established by this channel.

Using 200 kv., 25 ma. and 50 cm. target distance with 0.485 copper plus 1 mm. filtration, 100 r units were administered over an area sufficiently large to include the ear, mastoid region and posterior nasopharynx. Most of the patients required only 1 treatment. If the condition responded slowly and if immediate operation was not indicated, a second treatment was given within 48 to 72 hours. Of the 30 patients treated, 25 had 1 treatment each and 5 had 2 treatments each.

The irradiation seemed to be of distinct value in relieving the acute symptoms and in shortening the course of the disease. The average duration for the acute, purulent, uncomplicated cases was shortened 6 days, while that of the complicated cases was shortened 16 days. The clinical improvement when the treatment was effective was much more striking than these figures would indicate. The necessity for operation apparently was reduced.

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ORIGINAL ARTICLES.

A LAW OF DENERVATION.*

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ABOUT 55 years ago Hughlings Jackson¹⁹ discriminated a hierarchy of functions in the central nervous system that could reasonably be regarded as having been developed in the course of vertebrate evolution. He pointed out that when there is a destructive lesion affecting higher functional levels a dissolution takes place, characterized by loss of control of the higher over the lower, and by an increased activity of the lower levels, now released from dominance from above. The idea that this excessive neuro-muscular display could be explained by "irritation," though it has persisted, was set at naught by Jackson's schema. He, himself, did not reject the concept of neuronal instability, produced by blocking of blood vessels, growth of tumors, or other pathological processes. Thus he explained the discharge of nerve impulses in the form of epilepsy which is known under his name. That he ever thought that the two conditions—release and hyperexcitability, both due to permanent damage—might combine to produce inordinate movements, is not clear. That possibility exists.

For some years workers in the Harvard Physiological Laboratory have been concerned with the increased sensitiveness to chemical stimuli which appears in structures which have lost their proper nervous connections. Studies first made on peripheral organs have recently been extended to the nervous system. With respect for Hughlings Jackson's classical contributions to this field of interest I propose to review our results and related results of other investigators. Because of the regularity of the appearance of the phenomenon in the various organs which have been studied, and also because

* The Hughlings Jackson Memorial Lecture, delivered at the Montreal Neurological Institute, McGill University, Wednesday, April, 19, 1939.

of conviction that, if tested in other organs the phenomenon would continue to be observed, I have ventured to suggest that we are concerned with a law of denervation. That law may be stated as follows. When in a series of efferent neurones a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.

In illustrating that law, let us note first what happens when smooth muscle is deprived of its stimulatory adrenergic fibers. If, for example, the dilator muscle of the iris, innervated by such fibers, has been paralyzed by their section and degeneration, the pupil, in certain conditions, is more widely dilated on the paralyzed side than on the normal side. This "paradoxical pupillary dilation" was long a mystery. In 1903, however, Anderson^{1a} proved that the extra withdrawal of the denervated iris, which attended emotional excitement, dyspnea and anesthesia, was due to a local stimulation of the paralyzed radial fibers. He noted, furthermore, a similar phenomenon in the denervated nictitating membrane. This paradox of a magnified contraction of muscles which were no longer under nervous government Anderson attributed to an increased excitability, but he offered no evidence as to the exciting agent. The next year, 1904, Meltzer and Auer²³ supplied that evidence. They observed that a day or two after removal of one superior cervical ganglion from rabbit or cat a selected dose of adrenaline caused a marked dilation of the pupil, and also a constriction of the blood vessels of the ear, on the operated side, but had no effect on the other side. These observations were soon confirmed by Elliott^{15a} who also noted that the retractor penis muscle and the smooth muscles of hairs and the nictitating membrane were all sensitized to adrenaline by loss of their sympathetic connections. It will be recalled that the paradoxical pupillary dilation accompanied emotional excitement and asphyxia. In 1911, de la Paz, Hoskins and I^{10,11} showed that in these states adrenaline is discharged into the blood stream—a fact which would explain the curious anomaly. And the next year Elliott^{15b} reported that slight excitement of a cat induced the paradoxical reaction in its denervated iris and that the phenomenon disappeared when the adrenal glands were removed.

Further advances in our knowledge of sensitization of smooth muscle when denervated were made by Hampel and by Simeone. Hampel¹⁷, by tracing the course of increasing sensitivity of the nictitating membrane after removal of the superior cervical ganglion, found that for about a week it became rapidly more responsive than the normal membrane to graded doses of adrenaline, and thereafter underwent a more gradual change until a maximal state was reached at the end of 14 to 16 days. This state may continue for many months. Simeone³² demonstrated, however, that if the nerve supply to a sympathetically denervated nictitating membrane

regenerates, the increased sensitiveness gradually declines and finally reaches its previous grade.

At this point it is pertinent to state definitely what is meant by "sensitization." When I remark that a tissue is rendered more than normally sensitive to a given substance—by an operation, for example—I mean that the doses of the substance required to yield a certain *submaximal* response after the operation are smaller than before; or that the submaximal responses to the same dose of the substance are larger on the sensitized side than on the normal side. The *maximal* contractions of the denervated and the control innervated membrane are practically equal. Only when the contractions are submaximal, of course, is there opportunity for the appearance of increased sensitivity or increased irritability or excitability as manifest in the response.

Now let us return to our examination of the results of nerve degeneration. An effect quite as remarkable as sensitization by cutting the ultimate adrenergic fibers is a moderate sensitization by cutting preganglionic fibers. Elliott observed this effect in 1905; after extirpating a stellate ganglion he noted that adrenaline was a stronger stimulus for the iris, blood vessels and hair muscles on the decentralized than on the intact side of the head. And Hampel found that section of preganglionic fibers resulted in a course of sensitization of the nictitating membrane, which, though having the same time relations as when postganglionic fibers were destroyed, was only about half as great. If in these conditions a maximal state had been reached, removal of the ganglion was followed by a second increase of sensitivity, which again passed through rapid and later gradual stages. The final level of heightened responsiveness was about equal to that reached by direct denervation without previous decentralization.

The augmented sensitiveness of smooth muscle disconnected from the spinal cord has importance for clinical problems. In Raynaud's disease, for example, denervation of the over-contracted vascular muscle may abolish its spasm, but, as Freeman, Smithwick and White¹⁶ have shown, the muscle becomes exquisitely responsive to circulating adrenaline. Furthermore, the evidence is now clear that by means of decentralization the constricted state of the vessels can be overcome, without rendering them extremely subject to a circulating adrenaline (cf. White³⁵). This is exactly concordant with Hampel's observations.

We have seen that when *stimulatory* adrenergic fibers degenerate, the smooth muscle which they formerly supplied becomes more than normally responsive to adrenaline. The same condition is true for sympathin, the circulating chemical agent present in the blood after sympathetic stimulation, as Partington²⁴ has demonstrated. The question now arises, is destruction of *inhibitory* adrenergic fibers followed by a greater effectiveness of adrenaline in eliciting inhibi-

tion? The answer to that question was sought by Luco.²¹ Elliott¹⁵ had testified that he had not observed greater ease of inhibition as a sequel to denervation, and Langley and Magnus²⁰ had reported normal reactions to adrenaline in these circumstances. After allowing ample time for degeneration Luco recorded contractions of loops of rabbit intestine; they clearly revealed that the portion long deprived of its sympathetic nerves was more readily and persistently inhibited by adrenaline than were the portions freshly denervated. These tests were confirmed on the non-pregnant cat uterus, which is made to relax by adrenaline. Luco found that isolation of one of the uterine horns from connection with the hypogastric nerves resulted, after 8 or 9 days, in its being more responsive than the control contralateral horn to the inhibitory action of adrenaline—an effect recorded both *in vivo* and *in vitro*. Luco's observations on rabbit intestine have been supported by Youmans³⁶ who states that by denervation a loop of dog intestine may be made more than three times as responsive to adrenaline as a normally innervated loop. It appears, therefore, that severance of either stimulatory or inhibitory adrenergic fibers is followed by sensitization of the denervated smooth muscle to natural chemical agents.

Smooth muscle is supplied also with cholinergic fibers which belong chiefly to the parasympathetic divisions of the autonomic system. When these fibers are severed and degenerate, does the muscle become sensitized to the natural chemical mediator, acetylcholine? In 1905 Anderson^{1b} demonstrated that degeneration of the short ciliary nerves, after removal of the ciliary ganglion, was accompanied by an increased responsiveness of the paralyzed pupillo-constrictor muscle to pilocarpine. Since that drug mimics parasympathetic impulses there was a high degree of probability that there would be a similar response to acetylcholine. Shen and I³⁰ found that to be true. When we instilled a strong solution of acetylcholine (1 to 5 %) into the conjunctival sac, there was no effect on the normal iris. After excision of the ciliary ganglion, however, and delay for deterioration of the nerve filaments, instillation of the same solution caused a striking constriction of the paralyzed sphincter. On this sensitized muscle a more dilute solution of acetylcholine (0.1 to 0.01 %) was ineffective. After previous treatment with eserine, which protects acetylcholine from rapid destruction by a cholinesterase, the dilute solution produced a marked contraction. This myotic action of the drug could not have been due to eserine, for, as Anderson showed, eserine has no influence on the iris sphincter if its nerve supply has degenerated. To smooth muscle rendered more responsive to adrenaline when its adrenergic fibers are destroyed one may add, therefore, smooth muscle sensitized to pilocarpine and acetylcholine by destruction of its cholinergic fibers.

We now turn to a consideration of glands. Do they likewise

respond to a greater degree to chemical stimuli after they have been freed from nervous control? Evidence on this point has come from studies on the lachrymal gland and the submaxillary. Maes²² found that the secretion of tears was increased by intravenous injections of adrenaline, pilocarpine or acetylcholine. Removal of the superior cervical ganglion caused no immediate change in the response of the sympathetically denervated gland, but if the tests were made 11 days or more after the operation the drugs induced a considerably greater secretion on the denervated than on the control side. In obtaining these results Maes had to collect the fluid in the conjunctival sac by means of bibulous paper, of standard size, left in place for a uniform period, and accurately compared as to weight before and after the exposure.

The submaxillary is a more satisfactory gland to study, because its secretion can be registered directly by cannulation of the duct, and furthermore its status can be examined after a fairly easy exclusion of either the sympathetic or the parasympathetic control. Simeone and Maes³³ excised one superior cervical ganglion in the cat—an animal in which sympathetic impulses evoke submaxillary secretion. Many days (47 to 90) after this operation they determined the effects of intravenous injections of adrenaline, acetylcholine and pilocarpine on the salivary flow from the two glands, one previously, the other freshly denervated. In a few instances the output was approximately equal, but in the great majority of the tests the gland long deprived of its sympathetic nerves discharged much more saliva than its fellow—after adrenaline an increase commonly above 50%, after acetylcholine an increase ranging from 15 to 50%, and after pilocarpine 100% greater than the control.

The influence of exclusion of parasympathetic impulses must be studied mainly by severance of preganglionic fibers, for only few of the final neurones have their cell bodies outside the gland. Pierce and Gregersen²⁶ severed the chorda tympani nerve on one side in dogs. Standard intravenous injections of pilocarpine had proved that, in normal conditions, the rates of secretion from the two submaxillary glands are identical. Within 6 days after its chorda tympani had been cut, however, the decentralized gland responded more readily to pilocarpine; the salivary flow not only appeared more promptly but also in greater amount than from the opposite control gland. The effect developed fully in 2 or 3 weeks, and was undiminished 6 months or even a year after the operation. Acetylcholine, curiously, was reported as having a depressant influence. Special attention was not given to its action, however, and further study may resolve the anomaly. Enough is clear, however, to show that glands, like smooth muscle, become more readily responsive to chemical agents when deprived of their nervous connections.

A point which may now be considered is that denervated structures become more responsive not only to the agents which are their

natural stimulants, *e.g.*, adrenaline and acetylcholine, but to other agents as well. Thus, Rosenblueth²⁸ found that the nictitating membrane, after loss of its adrenergic fibers, was superexcitable to adrenaline, of course, but also to acetylcholine, pilocarpine and eserine. The lachrymal and submaxillary glands, when denervated or decentralized, likewise show a lack of specificity in relation to the stimulus which evokes the excessive response. This fact will be illustrated further as we proceed to examine the results of denervation on skeletal muscle and on nerve cells.

First, skeletal muscle. In 1863, Philipeaux and Vulpian²⁵ reported the puzzling fact that after severance and degeneration of the hypoglossal nerve, stimulation of the lingual nerve, ordinarily without effect, causes a slow response of the denervated muscles of the tongue. This effect was proved to be due to some influence contributed by the chorda tympani. Phenomena similar to this Vulpian reaction were observed by Rogowicz,²⁷ who noted a sluggish movement of denervated facial muscles when the cervical sympathetic was stimulated, and by Sherrington,³¹ who saw a like "pseudomotor" effect in muscles of the hind limb of a cat after the motor fibers had degenerated and the peripheral nerve was then stimulated. During the past 10 years the mystery of this phenomenon has been explained by accumulated evidence that it results from a leak of acetylcholine from the smooth muscles of blood vessels when they are affected through cholinergic fibers. This response does not ordinarily occur because, normally, skeletal muscle is not excited by the concentration of acetylcholine which is set free from the vascular muscles. When the motor nerves of a skeletal muscle have degenerated, however, it becomes sensitized. Then a local diffusion of acetylcholine, or an intravenous injection of it, both normally subthreshold, evokes in them the typical slow contracture.

The degree of increased sensitivity can be estimated. In the frog and fowl, the increase is about ten-fold (Brown and Harvey⁶); in the mammal, it may be as great as a thousand-fold (Brown, Dale, and Feldberg⁷). A curious manifestation associated with it has been reported by Bender.⁴ After severance of the facial nerve on one side in monkeys, and a delay of at least 6 days, fright induces a slowly developing persistent "contraction" of the denervated muscles. This fright reaction can be duplicated by an injection of acetylcholine and is intensified by protective eserine. The parallelism between the effects of fright and of acetylcholine is interpreted as indicating that the latter, secreted in the body during fright, is conveyed by the blood in sufficient concentration to influence the sensitized muscles. The source of acetylcholine which could produce the effect has not yet been learned.

That motor nerves of skeletal muscles are cholinergic was decisively proved by Dale and Feldberg¹³ in 1934. Sensitization to acetylcholine was therefore to be expected. But skeletal muscles

lacking their normal nerve supply become more responsive also to potassium chloride, nicotine and to other substances belonging to the nicotine group (cf. Dale and Gasser¹⁴). Again one notes that the greater responsiveness of the denervated structures is not related solely to the natural stimulus, but is manifest when other chemical agents are tried.

The next step in our inquiry was concerned with the sensitization of nerve cells. The final neurones of the sympathetic system, with cell bodies in the ganglia of that system, receive nerve impulses from the preganglionic fibers. At this neuro-neural junction acetylcholine serves as a mediator of transmission just as it does at the neuro-myal junction in skeletal muscle. Indeed, the events which occur at these two synapses are in many respects strikingly alike (cf. Rosenblueth and Cannon^{29a}). It is reasonable, therefore, to regard the ultimate sympathetic neurones as being innervated by the penultimate neurones. The question naturally arose, if the preganglionic fibers—those of the penultimate neurones—are cut and degenerate, are the final neurones sensitized to chemical stimulators?

An answer to that question was sought by Rosenblueth and myself in 1936. We used the nictitating membrane of the cat as an indicator. After severance of the preganglionic fibers in the cervical sympathetic strand on one side there was a wait of at least a week for degeneration of the severed axones; the animal was then anesthetized with "dial," the preganglionic fibers of the still intact contralateral sympathetic strand were cut, and both nictitating membranes were arranged to record simultaneously.

Two tests were applied. The first involved injection of acetylcholine intravenously. That required previous removal of the adrenal glands, because acetylcholine excites adrenal secretion, and secreted adrenaline acting on the nictitating membrane could confuse the result. Unfortunately; a number of preparatory drugs had to be employed: atropine to lessen the depressive action of acetylcholine on blood pressure, curare to prevent the peculiar stimulation of the extrinsic eye muscles by acetylcholine, and eserine to shield the injected acetylcholine from being destroyed by cholinesterase. After these preliminary steps were taken, an injection of 0.3 or 0.5 mg. of acetylcholine caused the membrane on the previously denervated side to undergo a quick contraction, followed by signs of an included slow contraction and thereupon a gradual relaxation; on the other hand, the membrane on the freshly denervated side did not shorten at all. After the superior cervical ganglia had been removed and the same doses were repeated, the quick contraction wholly disappeared and a slow contraction, which persisted, was much less than when the ganglia were present. The inferences were drawn that the quick, high response of the membrane supplied by the previously denervated ganglion cells was due to a discharge from these cells; and, since it did not occur on the side where the ganglion cells were

freshly denervated, that the responsive cells had acquired an increased sensitiveness to acetylcholine.

The defects in this evidence are two: first, the possibility of a differential effect of the preparatory drugs on the two sides, and second, the possibility of stimulating the sensitized membrane as well as the ganglion cells by the injected acetylcholine. In order to avoid these possible errors a much simpler method was devised—that of applying pledgets of cotton wet with acetylcholine (*e.g.*, 1% solution) directly to the exposed ganglia. After a brief latent period the nictitating membrane connected with the long denervated ganglion sharply contracted, while that connected with the opposite ganglion, just denervated, did not respond. It should be emphasized that as soon as the contraction was fully developed the pledgets were removed and the ganglia washed with normal salt solution. The test could then be repeated. That the unresponsive membrane was capable of contracting was proved by injecting adrenaline, and showing that it responded well, even though the corresponding contraction of the sensitized side was less than that induced by the pledget on the ganglion. If both ganglia were removed and the acetylcholine was applied on pledgets in their former positions, there was no effect. The special response on the previously cut side was not, therefore, due to transport of acetylcholine from the region of the ganglion to the membrane, but resulted from direct stimulation of the ganglion cells sensitized by degeneration of the preganglionic fibers which had formerly innervated them.

Such was the conclusion which Rosenblueth and I² drew from our experiments. The experiments were questioned, however, by Brücke, working in Dale's laboratory. There is no need to describe technical details of the differences between his methods and ours. That his results differed from ours was not surprising, for a number of reasons. First, in repeating our experiments of injecting acetylcholine he did not duplicate our conditions, for he omitted the use of curare, and that, we showed, significantly modified the results. Also, in repeating our experiments of locally applying the drug to the ganglia Brücke⁸ changed the conditions; he injected atropine (which has a depressant action on the response of the nictitating membrane), whereas we avoided use of any drug save the anesthetic. A further reason for Brücke's different results is that he gave mainly excessive doses of the stimulating substances. Thus, in experiments which he illustrated, he injected 30 to 70 γ of adrenaline, as contrasted with our more moderate amounts of less than 20 γ ; and to duplicate the effects of large doses of adrenaline he had to give large doses of acetylcholine, 2 to 5 mg., as contrasted with ours which were less than 1 mg. It is perhaps unnecessary to point out again that differences of sensitivity cannot be determined by tests which are not discriminative, but have maximal effects on both the more and the less sensitive structures. Finally, Brücke failed to

publish the time during which the pledgets wet with acetylcholine were applied to the ganglia; if that time is long, the effects are like those resulting from large doses—discrimination is absent, because the two sides, the more and the less excitable, are both stimulated to action.

In the face of this difference of testimony, however well justified the criticism of Brücke's experiments may be, another method was called for which would yield decisive results. The essential point was a separation of a direct action of acetylcholine on the nictitating membrane and an indirect action by way of the ganglion. A method assuring this required condition, and the results obtained by use of it, were reported by Rosenblueth and myself^{29b} in 1938. After preparing the previously denervated and the freshly denervated superior cervical ganglia we tied the external carotid arteries and made ready to inject acetylcholine into the common carotids. This arrangement had two definite advantages. First, it provided that the drug would have direct action on the ganglion, but required a devious course in the blood stream before there could be action on the membrane; thus the two effects were separated in time. Also, because of direct action on the ganglion, very small amounts of acetylcholine could be injected (5 to 10 thousandths of a milligram)—amounts so small that, while influential on the ganglion, they were without influence on the membrane depressed by atropine; thus, again, the effects on the two structures were separable.

Without atropine an injection of acetylcholine in adequate doses into either common carotid resulted in a contraction of the nictitating membrane in two stages—an initial sharp contraction having a latency of about 1 second, and a slower further contraction with a latency varying from 9 to 20 seconds. Similar injections after removal of the superior cervical ganglion resulted in complete disappearance of the initial sharp contraction, without modification of the delayed component. After atropine, with both ganglia in place, there was a slight reduction in the height of the initial component (but no change in the brief latent period) and an abolition of the delayed contraction. It is quite certain, therefore, that the quick initial rise in the record marks the response of the ganglion, while the belated rise is due to direct action of acetylcholine on the membrane.

Repeated tests on 7 animals proved that the previously denervated ganglion was consistently about four times more sensitive than its freshly denervated companion, *i. e.*, the threshold concentration of acetylcholine was only about one-fourth as great. In all these animals intravenous injections of adrenaline, which evoked responses on the previously denervated side equal to those caused by a small dose of acetylcholine, invariably elicited also a clear response on the control side. The evidence here presented demonstrates conclusively that the final sympathetic neurones, bereft of preganglionic fibers by

section and degeneration, become sensitized to their natural stimulating agent, acetylcholine.

Observations which Simeone, Rosenblueth and I³⁴ reported in 1938 have a significant bearing on the results just described and also on the next development of this series of studies. We examined the effect of partial denervation of the superior cervical ganglion. The rami communicantes of the first and second thoracic nerves were cut and time was allowed for the fibers to degenerate. According to Langley this procedure might be expected to cause a loss of 50% or more of the preganglionic fibers which supply the nictitating membrane. Some weeks after this operation the rami of T-1 and T-2 were cut on the control side, the thoracic sympathetic chains were crushed below T-4, and shielded electrodes were so placed on each chain as to include and stimulate the fibers from T-3 and T-4. The contractile response to equal stimulation of an approximately equal number of preganglionic fibers on the two sides was much greater from the partially denervated ganglion prepared previously than from the partially denervated ganglion prepared freshly. The greater contraction might be explained as due to repetitive discharge from cells in the isolated ganglion because the cholinesterase, known to disappear from the fully denervated ganglion, becomes insufficient for rapid destruction of acetylcholine, which therefore persists and continues to act. Or it might be explained as a consequence of stimulation of a larger number of slightly innervated cells—cells ordinarily in the “subliminal fringe,”—because they have become sensitized. Whatever the explanation the important fact emerges that partial denervation of ganglion cells renders them more highly responsive—an effect which, from what we know of total denervation, can reasonably be attributed to destruction of preganglionic fibers.

The sensitizing of ganglion cells by denervation or partial denervation naturally suggested that the nerve cells of the brain and spinal cord might be sensitized if they were “denervated,” *i. e.*, deprived wholly or in part of the nervous connections from which they routinely receive impulses. As a region for testing this idea Haimovici and I⁹ selected the lower portion of the spinal cord, for a number of reasons. First, semisection of the cord interrupts descending fibers of the cut side without noteworthy effects on the opposite side. Again, the operation is relatively simple and well borne. Furthermore, a single muscle, the quadriceps, attached to the patella and supplied by a readily accessible nerve, can be easily isolated and used as an indicator of nervous discharges. In addition, by means of a thread looped about the end of the aorta the direct blood supply to the muscle can be promptly and temporarily shut off while that to the cord is continued. And finally, injection into the lower thoracic aorta permits chemical agents to be delivered locally to both sides of the cord in a concentration not affecting the rest of the nervous system.

Accordingly the spinal cord was semisected, aseptically, above the sacral enlargement and, after a wait of at least five days to allow the severed axones to degenerate, the animal was prepared for the acute experiment. Under ether anesthesia the brain was pithed, the two quadriceps were arranged for recording and the aorta was exposed in the lower thorax for injections. To simplify the muscular responses most of the leg muscles were paralyzed by severance of the sciatic nerves. Each quadriceps pulled against a rubber band attached to the writing lever. The intact side of the cord was not cut, because after the brain was pithed there was no evidence of superior influences affecting the sacral centers, also because cutting the cord freshly was shown to have a depressant effect, and finally because, with the cord previously semisected on one side and semisected only one day on the other side, differences were recorded from the two sides which were the same as if the control side had been left intact.

When strychnine sulphate was injected into the lower aorta there resulted many more jerks on the cut than on the control side, or an appearance of clonus on the cut side which was more continuous and more persistent than on the opposite side. In one instance the clonus on the cut side persisted for 68 minutes, at the rate of about 13.5 contractions per second, thus yielding a total of more than 55,000 contractions, while the intact half of the cord was quite inactive.

Injections of acetylcholine, when the femoral nerve was severed, revealed the interesting fact that the quadriceps on the cut side is sensitized to that chemical agent. That acetylcholine, however, stimulates the cells of the spinal cord can be shown by blocking the direct blood flow to the recording muscles (the femoral nerves being intact, of course) and then injecting; with a properly selected dose there is a response on the cut side but not on the intact side, as indicated by the muscular contractions. And, if now nervous and vascular connections are left undisturbed, an injection of acetylcholine brings forth a striking effect—a combination of the direct muscular and the neuronal stimulations, much more marked on the semisected than on the other side.

Strong salt solutions are known to have convulsant action on the central nervous system. When a small amount of a half-saturated solution of sodium carbonate is injected into the aorta, the effect is outstanding on the semisected side and only slightly present on the intact side.

Perhaps the most striking mode of displaying the difference in sensitivity of the quadriceps centers on the two sides of the cord is by inducing asphyxia. This mild procedure can be repeatedly used. The asphyxial state consistently provokes a much more remarkable reaction on the cut side.

In these various experiments there were controls, by section of the femoral nerves, which ruled out direct muscular stimulation,

and by frequent testing of the quadriceps jerk, which ruled out damage to the reflex centers. The inference was drawn, therefore, that, as neurones of the superior cervical ganglion are sensitized by severance and degeneration of nerve fibers which routinely deliver impulses to them, neurones of the spinal cord are analogously sensitized by partial exclusion of their normal nerve connections.

The phenomenon of sensitization of skeletal muscle to acetylcholine by severance of some fibers which innervate the ultimate motor neurones (Hoff¹⁸) appears to be analogous to the sensitization of the nictitating membrane to adrenaline by section of the pre-ganglionic fibers, and sensitization of the submaxillary gland to pilocarpine by cutting the chorda tympani nerve; in all three conditions damage to penultimate neurones results in a heightened responsiveness of the organ still connected with the ultimate neurones. There is some indication that the peripheral effect may be produced at least one step further back in the neuronal series, for Ascroft² discovered that when the cord is semisected at T-7—thereby interrupting antepenultimate or perhaps anterior neurones—the blood vessels of the foot on the cut side are especially responsive to adrenaline.

We have now seen that smooth muscle, whether normally stimulated by parasympathetic influences or stimulated or inhibited by sympathetic influences, is rendered more excitable to chemical agents by destruction of the ultimate innervating neurones. The same condition results when glands, subject to sympathetic impulses, or skeletal muscle, or peripheral or spinal neurones, are fully or, in some instances, partially denervated. And to some degree smooth muscle, glands and skeletal muscle are thus affected if penultimate, and possibly antepenultimate neurones are destroyed. These are pertinent instances of a law of denervation which I formulated earlier in this lecture. It is of historical interest that, in 1880, Claude Bernard,⁵ on the basis of relatively few observations, expressed the opinion that “the excitability of all tissues seems to augment when they are separated from the nervous influence which dominates them”—a remarkable instance of perspicacity.

The evidence that neurones in the spinal cord are sensitized by being separated from their proper controls naturally raises questions as to the effects of disappearance of neuronal paths elsewhere in the nervous system. I have no experiments to report on the cerebral cortex. Some observations by Bard,³ however, are highly suggestive. In cats, he removed surgically all the cortex on one side except the motor area of the frontal pole. The opposite cortex was left intact. The animals, after being studied for considerable periods, were lightly anesthetized with dial and then subjected to a cortical exploration. Electrical stimulation revealed a marked difference in the responses of the two sides. In 2 animals the isolated motor area had a threshold very much lower than the motor area on the intact

side; and in a third animal stimulation of either the foreleg or hind-leg area in the cortical remnant resulted in a vigorous and prolonged after-discharge involving both legs. Similar stimulation of the intact motor cortex had no such effects. Of course, the much augmented sensitiveness and the marked after-discharge, reported by Bard, may have been due to release of the isolated motor area from inhibitory influences. From what we have learned from other "denervations," however, it seems not unreasonable to infer that the cortico-spinal neurones and perhaps subordinate neurones have been rendered more excitable to electrical stimuli by loss of contacts with other neurones which formerly delivered impulses to them. A superirritable state may, of course, play a rôle even though release from inhibition is also a factor in the peculiar increase of responsiveness.

In discussing epilepsy, Jackson wrote of the "discharging lesion" as a "physiological fulminate," *i. e.*, the normal cells of a center becoming a hyperfunctioning part of it. Thus, there may be an abrupt and excessive local discharge from some highly unstable part of the cerebral hemisphere. What produces the instability? As already noted, Jackson suggested that tumors or blocking of blood vessels might produce it. "No one can suppose that a tumor discharges," he wrote; "the tumor leads to instability of the grey matter" and "the discharge causing the convulsion is of this unstable grey matter." Is it not possible that tumors, and such lesions of the motor area of the cortex as are associated with the name of Hughlings Jackson, may induce instability of the neighboring cortical cells by destroying their connections with other cortical cells? If that should prove to be true, it would be another illustration of the law of sensitization of denervated structures which I have endeavored to illustrate. Here is work to be done—work in which the great neurologist whom we memorialize today would be deeply interested.

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BLOOD VISCOSITY.

WITH SPECIAL REFERENCE TO CAPILLARY, ARTERIAL (APPROXIMATE), AND VENOUS BLOOD SPECIMENS.

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DURING the past 30 years considerable discussion has appeared in the literature concerning the relationship between the size and number of blood cells and blood viscosity.

In 1911 Hess,⁵ using his viscosimeter, studied suspensions of particles "like red blood cells" in varying proportions in plasma. The plotted curve showed that with increase in the number of particles, the viscosity rose. Reference was made to a similar curve obtained by Blunschy who worked with erythrocytes. Langstroth⁷ showed in 1911 that venous stasis produced by a tourniquet to the arm was accompanied by an increase in the relative volume of erythrocytes and a rise in the viscosity of a venous blood sample. Bircher² in 1921 revived interest in the instrument of Hess. Among other points he asserted that blood viscosity is directly related to total red cell volume. Nine years later Harris and McLoughlin⁴ wrote in regard to their series of hypertensive patients that blood viscosity could not be correlated with the number, diameter, or volume index of red cells. More recently, however, Baldes, Essex, and Markowitz¹ have shown that crotalin causes red cells to swell and that with their greater volume, the viscosity of the blood increases. Tanaka¹² obtained similar results using suspensions of erythrocytes in solutions of varying saline concentrations. Furthermore, Markson⁸ has presented data on a group of patients with congestive heart failure, indicating that blood viscosity varies directly with the size and number of red blood cells. Finally, Nygaard,

Wilder, and Berkson⁹ have demonstrated that the relation between blood viscosity and the relative volume of erythrocytes (hematocrit value) can be expressed by linear formulas. Stephens¹¹ has shown that similar curves are obtainable using suspensions of white blood cells in plasma.

Our purpose has been to study the relationship between red cell count and viscosity and to determine the possible influence of the hemoglobin content of the cells; to establish normal viscosity values; to compare red cell counts and viscosities of capillary, arterial (approximate), and venous specimens taken nearly simultaneously from the same subject; and finally, to combine viscosity and venous pressure tests.

Method. The Hess^{5a} viscosimeter was the instrument chosen for this study because the originator had defended it so successfully from early criticism,^{5c,d,e,g} because many investigators^{2,4,8,9,11} have used this type and found it satisfactory, and because the apparatus lends itself nicely to bedside manipulation.

The technique employed was fundamentally that described in the pamphlet accompanying the apparatus dispensed by Arthur H. Thomas Company, Philadelphia. Special attention was paid to having the patient rub his hands together in "hot water (about 40° C)" for at least 5 minutes in order to produce "active hyperemia." The middle finger tip was usually selected. Ether was used to clean and dry the skin. The stab wound was made sufficiently deep with a triangularly pointed suture needle so that the blood would well up freely with minimal or no squeezing of the finger. Such a specimen was considered to be approximately arterial in origin. The blood reservoir tube was quickly filled; and the viscosity, determined. Then from a fresh drop of blood the red cell counting pipette and hemoglobin pipette were filled.

Variations in the above procedure were admitted only in obtaining capillary and venous blood samples. The withdrawal of capillary blood differed in that no attempt was made to produce hyperemia. Venous blood was obtained from the cubital or median veins. About 4 cc. were withdrawn, using a 21-gauge needle fitted to a 5-cc. syringe, and immediately transferred to a small flat bottom glass container. From the latter, the blood was sucked into the reservoir tube of the viscosimeter by means of the rubber attachment of a hemocytometer pipette. The viscosity was promptly determined by one of us (V. W.), while the other filled the pipettes for red cell and hemoglobin tests. The time required for these procedures was sufficiently short to obviate the need for an anticoagulant. The tourniquet was tightened around the upper arm only long enough to allow puncturing the vein and was removed before the blood was withdrawn. The glassware was kept chemically clean and was thoroughly dried before use.

For the red cell counts a Levy-Hausser counting chamber was used. Each determination represented an average of 2 counts with a variation of less than 10%. In counts over 6 million it was found helpful to make dilutions of 1 to 333 $\frac{1}{3}$ instead of 1 to 200, by drawing the blood to 0.3 rather than the 0.5 mark on the pipette. The sum of the cells in 80 small squares of the chamber was multiplied by 5/3, and then 4 ciphers were added to give the count per cubic millimeter. The Haden-Hausser hemoglobinometer (laboratory model) was employed, 15.4 gm. of hemoglobin representing 100%. The venous pressure determinations were made by the direct method using the apparatus of Griffith, Chamberlain, and Kitchell² and the technique described by Holbrook.⁶

Standardization in these studies was maintained with rare exception in the following manner: one of us (V. W.) made all the viscosity tests and blood counts; the other (A. A. H.) took all the venous pressures. In the combination series the former determinations were usually made within 24 hours of the latter. Nearly all the examinations were carried out in the late morning just before luncheon.

The data presented below were obtained from a group of 118 individuals most of whom were medical students and nurses. For the most part their studies furnished the normal and control values.

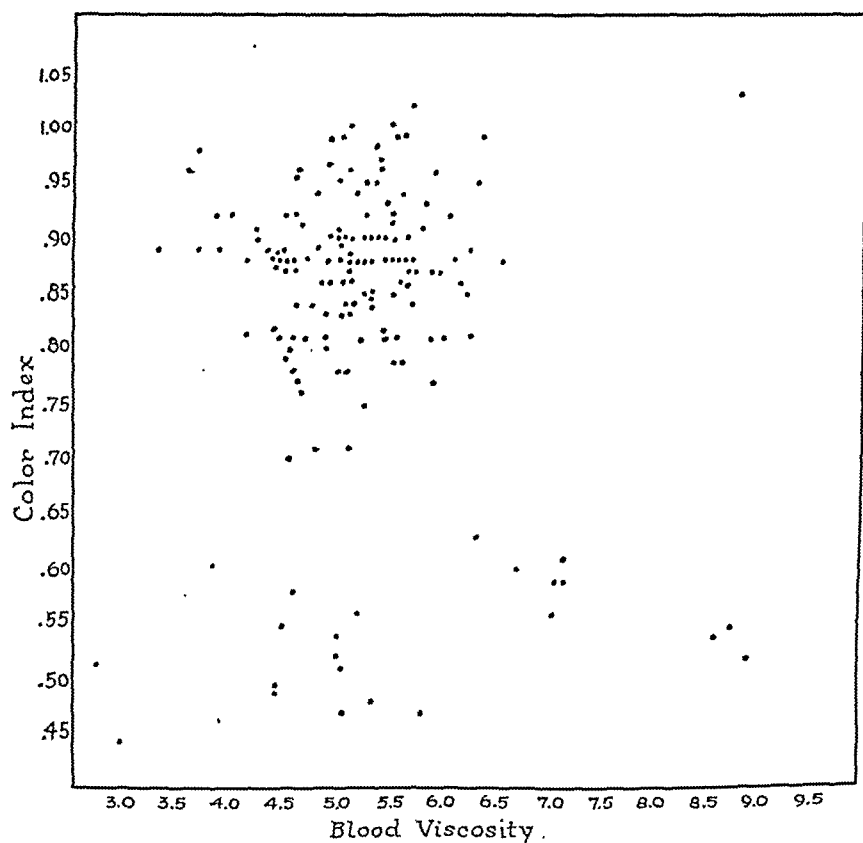


CHART 1.—Blood viscosity is plotted against color index. Red cell counts, hemoglobin and viscosity values were obtained, 160 times from 118 individuals.

The rest of the subjects were medical out-patients chosen because of abnormal counts. In all, there were 63 males and 55 females. The range in ages extended from 15 to 75 years as follows: 48 subjects between 15 to 30 years; 26 between 30 and 40; 27, 40 to 50; 8, 50 to 60; and 9 between 60 to 75.

From Chart 1 viscosity against color index, it can readily be seen that there is no correlation between these two variables. As would be expected, an entirely similar chart, not included here, resulted from plotting viscosity against hemoglobin values.

Chart 2 presents 164 red cell counts plotted against the corresponding viscosities. It is apparent that there is a direct relation between red cell count and viscosity as shown by the linear grouping of the points.

The square in Chart 2 is drawn to encompass what we have arbitrarily chosen as normal values. Ninety-seven cases are represented in this area with 121 determinations indicated. The red cell count varies from 4,100,000 to 5,850,000 per c.mm.; and the viscosity, from 4 to 6.

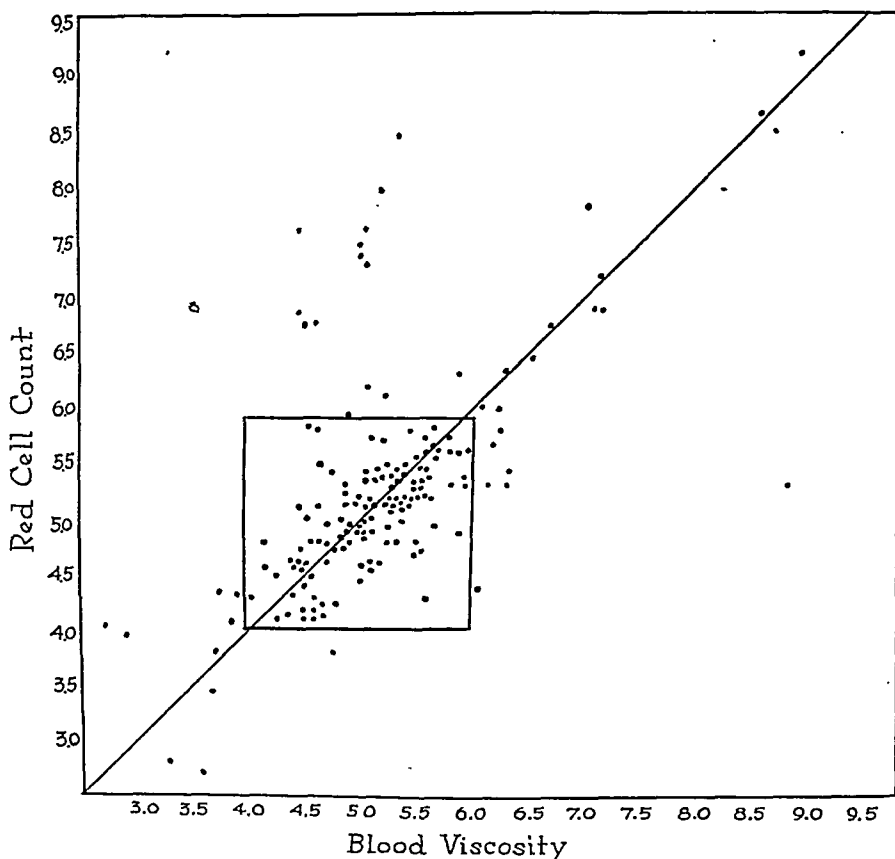


CHART 2.—Blood viscosity is plotted against red cell count (millions per c.mm.). There are 164 points representing determinations on 118 individuals.

Chart 3 expresses in a different way the data contained within the square of Chart 2. Among the 97 individuals in this group there were 19 upon whom more than one test was done. For each of these cases the figures were averaged and arranged in Chart 3 to show their distribution within the limits defined as normal. It will be seen that the tendency is toward a hyperbolic curve. Sixty-nine per cent of the cases have red cell counts between 4,500,000 and 5,500,000 per c.mm.; and 65% have blood viscosities between 4.6 and 5.6. The average red cell count for the 97 subjects was 5,020,000; the average viscosity, 5.08.

Chart 4 gives the results of capillary, arterial (approximate), and venous red cell counts plotted against their respective viscosities. This combination of 6 determinations done within a few minutes of each other was made 31 times on 19 patients. The points fell in the same general distribution as those shown in Chart 2. On studying the figures to see which of each group of 3 points came closest to the diagonal line, it was found that the capillary was closest in 8 instances; the venous, in 10; and the arterial, in 15. It happened twice that the venous point was as close as the arterial.

No regularity, however, was observed in the differences encountered between the capillary, arterial, and venous red counts and viscosities either on repeated tests of the same individual or on considering the study as a whole. For example, comparison of the

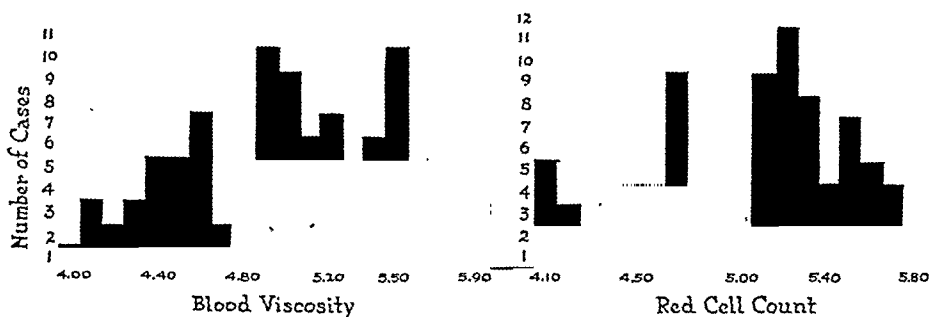


CHART 3.—This chart represents the data within the small square in Chart 2, which was drawn arbitrarily to include normal figures. Thus, the distribution over the normal ranges of blood viscosity and red cell values is shown graphically for 97 cases.

31 capillary, arterial, and venous red cell counts brings out that the relative heights of the counts occur in no regular proportion. This is shown in the following table in which the various combinations are arranged in order of diminishing values from left to right. Thus, the first line indicates that in 6 instances the venous count (V) was higher than the arterial (A) and the arterial, higher than the capillary (C).

V > A > C : 6 times

C > V > A : 7 times

V > C > A : 7 times

A > V > C : 3 times

C > A > V : 7 times

A > C > V : 1 time

Furthermore, if for each group of 3 tests the difference between the arterial and capillary counts is compared with the difference between the arterial and venous counts, the results show that the former is smaller than the latter 14 times; and greater, 17 times. Similar comparisons of the differences between capillary-arterial and capillary-venous counts on the one hand and venous-arterial and venous-capillary counts on the other hand, show again that the variations are nearly evenly divided between being greater and smaller.

Chart 5 represents the plotting of blood viscosity against venous pressure. These tests were given to 30 patients with normal venous pressures, 2 of whom were examined twice. From the distribution of the points one can find no tendency toward direct relation between blood viscosity and venous pressure.

Discussion. Attention was paid to hemoglobin values in this study, because of the assertions by Hess^{5b} and Blunschy that a parallel relationship exists between hemoglobin and viscosity. Hess expressed this relation in the formula $Q = \frac{\text{Hemoglobin}}{\text{Viscosity}}$, a quotient

of 17 to 21 being considered normal. From our studies expressed in part in Chart 1, we could discover no significant relation between hemoglobin and viscosity. Comparison of Chart 2 with Chart 1 indicates that it is the number of red blood cells which influences blood viscosity and not their hemoglobin content. Others^{1,8,9,12} have shown that the size of the erythrocytes is also a determining factor.

The pertinent data available from the literature on normal blood viscosity are given in the following table. Our material is included, and it will be seen that our average figure of 5.08 falls in the mid-zone between the figures given by the other investigators.

TABLE 1.

Author.	Type of instrument.	Age group (yrs.).	No. of normal cases.	No. of tests.	Viscosity.	
					Normal limits.	Average.
Bircher ²	Hess	10-80	Not given	Not given	4.2-4.9	Not given
Harris and McLoughlin ⁴	Hess	Not given	21	Not given	4.0-6.0	♂ 5.45 ♀ 5.3
Markson ⁸	Hess	Not given	30	Not given	4.0-6.0	5.32
Hess ^{5b}	Hess	20-80	Not given	124	♂ 4.3-5.3 ♀ 3.9-4.9	4.57
Holbrook and Watson	Hess	15-75	97	121	4.0-6.0	5.08

The studies on capillary, arterial (approximate), and venous blood and on venous pressure were conducted with the idea of determining whether or not the technique described by Hess for obtaining blood samples was entirely satisfactory. The statement is not infrequently found in the literature^{4,5b,8} that with circulatory stasis the CO₂ level of the blood rises and with it the viscosity, due to an increase in the size of the red cells. Langstroth⁷ has presented evidence to show that a rise in venous pressure increases the viscosity of venous blood not because of changes in the CO₂-O₂ propor-

tion but because of a concentrating effect on the cells due to loss of fluid into the tissues. Root, Thompson, and White¹⁰ have written that increased venous pressure produces a high venous red cell count and a low capillary count. These investigators and Langstroth have observed that normally there is no appreciable difference between capillary and venous red cell counts. It was because of the above considerations that we assembled the data presented in Charts 4 and 5.

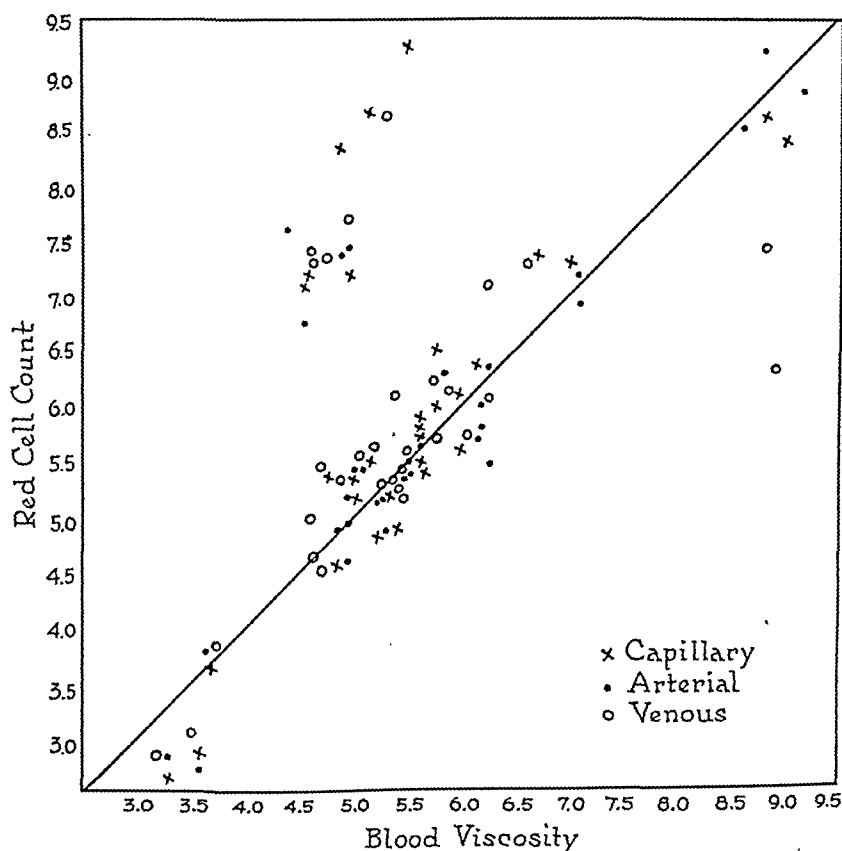


CHART 4.—Capillary, arterial (approximate), and venous red cell counts (millions per cmm.) are plotted against the viscosities of the respective blood samples; 31 such tests were performed on 19 patients.

We also found no significant differences between capillary and venous red counts and in addition the so-called arterial counts. Our charts show that the viscosity tends to increase in direct proportion to the red cell count no matter from what source the blood comes, and that venous pressures within normal limits apparently exert no influence on blood viscosity. Therefore, since the readings obtained according to the method of Hess (arterial in Chart 4) approach the theoretically normal line the closest, we conclude that this method is indeed satisfactory.

Conclusions. The conclusions to be drawn from our study and the reports in the literature may be given briefly as follows:

1. There is no correlation between blood viscosity and color index.
2. There is direct relation between the number of erythrocytes and blood viscosity.
3. The normal, average, blood viscosity value is about 5.

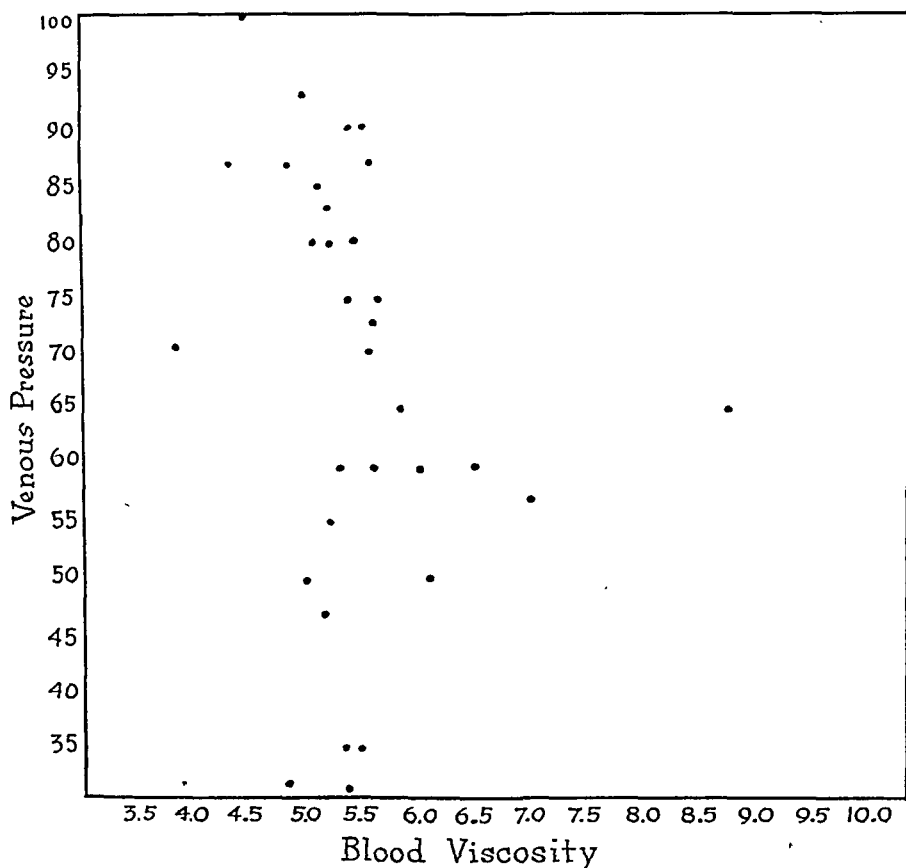


CHART 5.—Blood viscosity is plotted against venous pressure (in millimeters of water).
Thirty-two tests were made on 30 individuals.

4. The blood samples taken from a finger tip in which hyperemia has been produced (so-called "arterial" blood) give as reliable results as capillary or venous specimens.

5. There is no correlation between venous pressure within normal limits and blood viscosity.

6. Comparative studies of capillary, arterial, and venous bloods indicate that this method gives entirely satisfactory results.

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CLINICO-HEMATOLOGIC EVALUATION OF BONE MARROW BIOPSIES.

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It has become manifest that the study of bone marrow may, in certain instances, be of material aid in the diagnosis of blood dyscrasias and other diseases, when these studies are correlated with the peripheral hemocytology.

The interpretation of the bone-marrow findings may be studied in disorders of the following apparatus: 1, leukopoietic; 2, erythropoietic; 3, thrombocytopoietic; 4, reticulo-endothelial.

Sufficient information has been gathered in this review, based on 275 bone-marrow studies, to form a basis for the concise evaluation of the bone-marrow fluid, obtained by sternal bone-marrow aspiration.¹⁵

Normal bone marrow was obtained from 28 individuals free of infection, hemorrhage, malignancy or other diseases, as ascertained by complete history, physical, laboratory and roentgenologic examinations. The study of the marrow consisted of a differential of the cellular elements, noting especially the hematologic criteria.

Compared with other tables of normals, this study was in almost complete agreement with other authors.²⁰ There is some difference in the enumeration of the staff forms. It appears that what were recorded as neutrophils in this study were regarded as staffs by others. Arinkin and others,²⁰ however, include both under polys, bringing their results in close agreement with our findings. There is a significant practical difference, inasmuch as, according to figures here presented, the left shift will be found less in this study as compared to those studies in which staff forms are given high normal values.

It is fortunate that in this series, clinical investigations, which included infections, were in perfect consonance with our findings. One is therefore justified in accepting these results as practical for

the study of clinical material. There are no material differences noted as far as erythrocytes, lymphocytes, or plasma cells are concerned (Plate 1).

Leukopoiesis, including left shift, could be ascertained by noting the relationship of the early white cells and the late white cells (neutrophils, eosinophils and basophils). In 100 cells (or multiples of 100 cells) thus counted, one found normally about 55 early cells and 45 late cells, *i. e.*, the non-segmented-segmented (N:S:S) ratio was 55:45. An increase of the early cells produced a left shift, an increase in the late cells a right shift. The former was encountered in hemorrhages, infections, myeloid leukemia, and so forth, the latter in Hodgkin's disease, polycythemia vera, pernicious anemia and in normal cases.

ERYTHROPOIESIS. A. *Erythrogenesis* was evaluated by noting the relationship of the total white cell population of the bone marrow to its erythroblastic elements. Under normal conditions, if 100 cells (or multiples of 100 cells) were counted, the average obtained was 85 of the white cell series to 15 of the erythroblastic series, *i. e.*, the granulocyte-erythroid (G:E) ratio was 85:15. An increase in the latter bespoke an increase in erythrogenesis. In some cases, particularly hemolytic icterus, pernicious anemia in relapse, Cooley's anemia, sickle-cell anemia, and so forth, this ratio was reversed.

B. *Maturation of erythroblasts* was determined by noting the relationship between the number of early erythroblasts to the late erythroblasts (normoblasts) (Table 1). Normally this erythroblast-

TABLE 1.—CLASSIFICATION OF THE RED BLOOD CELLS.

Cell type.	Nucleus.	Cytoplasm.		
		Non-hemo- globiniferous. Basophilic.	Hemoglobiniferous.	
			Poly- chromatic.	Eosino- philic.
Erythroblast:				
Megaloblast . .	Delicate network with nucleolus	+	0	0
Macro-normoblast A	Delicate network	0	+	0
Macro-normoblast B	Coarse network	0	0	+
Macro-normoblast C	Cartwheel	0	0	+
Normoblast:				
Normoblast A . .	Pyknosis	0	0	+
Normoblast B . .	Extrusion	0	0	+

normoblast (E:N) ratio was 15:85. An increase of the former was evidence of a defect in maturation. This was seen in hemolytic icterus, pernicious anemia in relapse, Cooley's anemia, sickle-cell anemia, cases of liver damage, intestinal obstruction, uremia, carcinoma of the stomach, and so on.

Other bone-marrow constituents, not included in the differential, were lymphocytes, reticulum cells, plasma cells, megakaryocytes, malignant, Niemann-Pick and Gaucher cells. The lymphocytes numbered normally about 10 to every 100 white cell counts, *i. e.*,

the myeloid:lymphoid (My:Ly) ratio was 90:10. In lymphatic leukemia the My:Ly ratio was reversed, *i. e.*, 10:90. Occasionally, in infectious mononucleosis and agranulocytosis the number of lymphocytes was increased. Reticulum cells, noted occasionally in the smears, were particularly evident in Hodgkin's disease. Plasma cells were present usually about 2 or 3 per 100 white blood cells. The latter were especially prominent in multiple myeloma and aplastic anemia (benzol poisoning). Other unusual cells seen in the bone marrow in certain cases were Niemann-Pick, Gaucher and malignant cells. Megakaryocytes were sparse in the bone marrow, usually 1 or 2 were found on a smear. A marked increase in number was found in thrombocytopenic purpura and Hodgkin's disease.

DISEASES OF THE LEUKOPOIETIC MECHANISM. In disorders of the leukopoietic mechanism the N:S:S and the G:E ratios served as distinguishing landmarks; the former to determine the degree of left shift of the white cell series and the latter the extent of erythrogenesis.

A. Leukemia, Myeloid. There was a greater left shift of the white blood cells in the acute than in the chronic cases. Erythrogenesis was depressed²³ in the acute more than in the chronic cases. Since at times it was difficult to differentiate between a chronic myeloid leukemia and a leukemoid reaction secondary to hemorrhage, infection or malignancy, the following two points were found of value. There was a selective left shift in the chronic myeloid leukemias, *i. e.*, predominantly premyelocytic. Erythrogenesis was increased in leukemoid reactions but diminished in the leukemias.

Agranulocytosis and infectious mononucleosis frequently required differentiation. In the former, myeloblasts, predominant in the bone marrow, did not appear in the peripheral smear. In other words, there was, in addition to a maturative arrest of leukogenesis, a definite arrest in delivery of the white blood cells. In infectious mononucleosis there was not as marked a left shift of the N:S:S ratio but occasionally the lymphocytes were increased in number. In addition, one noted the peculiar lymphocytes seen in glandular fever.²⁰

TABLE 2.—BONE MARROW CYTOLOGIC ELEMENTS.

1. Myeloblasts are large cells of the myeloid series with a finely reticulated nucleus containing nucleoli surrounded by a rim of deep blue homogeneous cytoplasm but with no definite specific granulations.

2. Myelocytes are cells of the myeloid series with beginning or definite specific granulations in the cytoplasm; nucleus is more homogeneous or clumpy. (Premyelocytes included.)

3. Metamyelocytes are cells of the myeloid series with well-defined nuclear indentation without staff formation, but with definite immature specific granulations.

4. Staff cells are non-lobulated myelocytic elements with mature specific granulations.

5. Polys are segmented neutrophilic cells with mature specific granulations.

6. Gaucher cells are large mononuclear cells, 10 to 15 times the size of a red blood cell (approximately 70 to 150 microns) with a nucleus which has dense or coarse

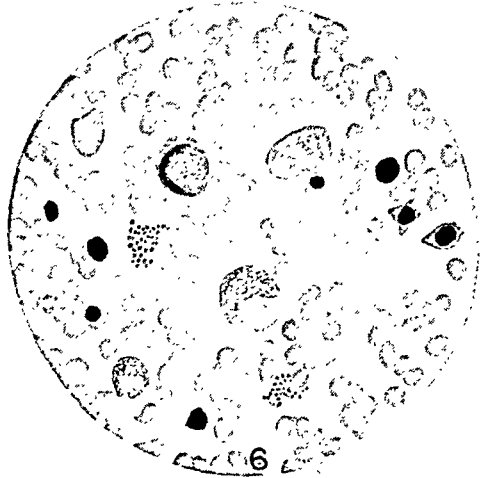
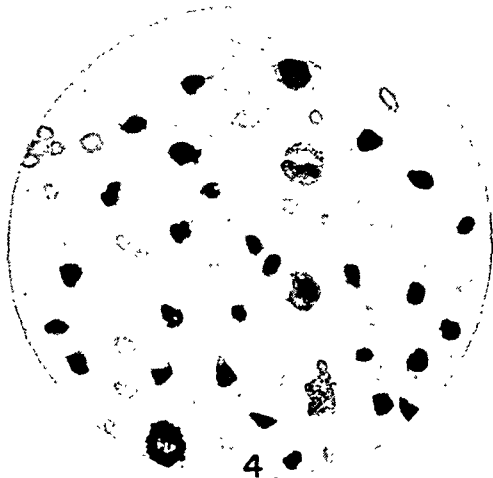
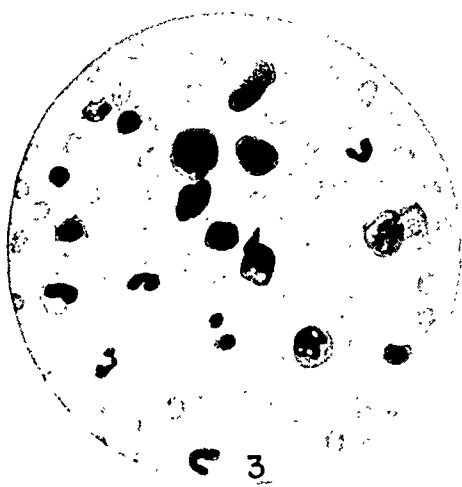
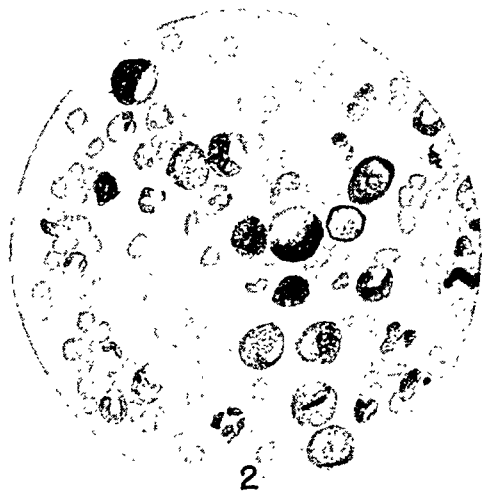
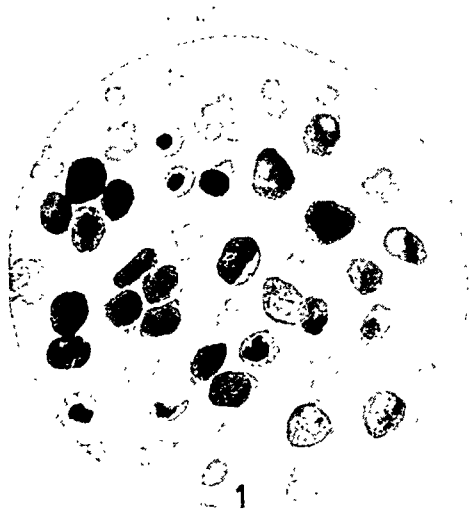


PLATE 1.—Fig. 1, Acute myeloid leukemia.
 Fig. 2, Chronic myeloid leukemia.
 Fig. 3, Infectious mononucleosis.
 Fig. 4, Lymphatic leukemia.
 Fig. 5, Hodgkin's disease.
 Fig. 6, Agranulocytosis.

In both plates the illustrations are photographs of water colors.

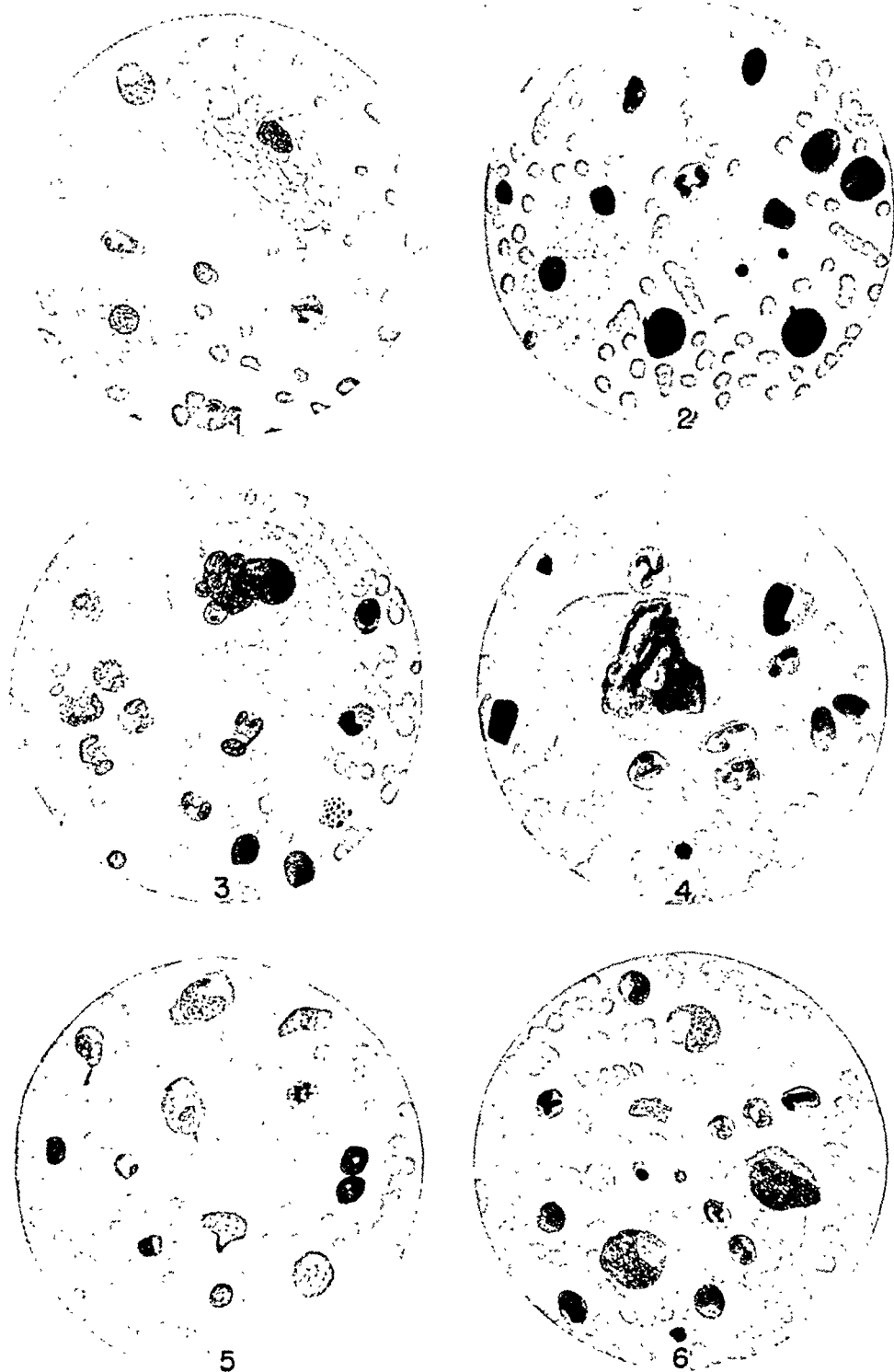


PLATE 2.—Fig. 1, Gaucher's disease.
 Fig. 2, Niemann-Pick's disease.
 Fig. 3, Eosinophilia with megakaryocyte.
 Fig. 4, Purpura hemorrhagica with megakaryocyte.
 Fig. 5, Plasma cell myeloma.
 Fig. 6, Spastic paraplegia (Ferrata cell).

chromatin giving it a lymphatic appearance. The nucleus is round, central or eccentric, has no perinuclear halo and is surrounded by cytoplasm filled with an abundant fibrillary meshwork which gives the appearance of lack of substance. At times one may see engulfed red or white cell elements demonstrating its phagocytic propensities.

7. Niemann-Pick cells are slightly smaller than Gaucher cells. The nucleus resembles that of the Gaucher cell, may be central or eccentrically placed and is surrounded by abundant cytoplasm characterized by its foamy appearance. Phagocytosis of blood cells is sometimes demonstrable in the cytoplasm of the cells.

8. Reticulum cells are large mononuclear cells, irregular in outline, about two-thirds the size of Gaucher cells, and possess an irregularly shaped nucleus but no nucleoli. The nuclear chromatin is coarse and dense, stains blue-red with Wright's stain and occupies the greater part of the cell. The cytoplasm is abundant, sometimes vacuolated, and possesses a faint sky-blue color.

9. Ferrata cells are about the same size as reticulum cells. Both cell body and nucleus are irregular in outline. The latter has a fine meshwork and usually possesses nucleoli, resembling in this respect a myeloblastic nucleus. The cytoplasm is faintly sky-blue and has at times many azurophilic granulations.

10. Carcinoma cells appear as large epithelial elements, usually mononuclear and sometimes as a double nucleus. The nuclei tend to be round with coarse chromatin resembling a lymphocyte, and usually have a central dark-staining area. The cytoplasm is very faint with a slight red to purple tint (Wright's stain). These cells are usually seen in clusters in a syncytium-like arrangement.

11. Plasma cells are mononuclear cells varying in size from 7 to 20 microns with a deeply basophilic, eccentric nucleus which at times may have a cartwheel arrangement of the chromatin. There is oftentimes a perinuclear halo. The cytoplasm is deeply basophilic and appears smooth and glassy. Certain areas of the cytoplasm take the blue stain in great concentration and appear blotchy. The outline of the cell is irregular, pyriform or stellate; there are no granules in the cytoplasm.

12. Infectious mononucleosis cells are lymphocytic cells, 2 to 3 times the size of red blood cells. The nucleus is round and is more or less indented. The cytoplasm is relatively abundant, and is deeply basophilic. There may be azurophilia in the cytoplasm. Because of the shape of the nucleus and the relative abundance of the cytoplasm, the cell appears at times like a monocyte so that "monocytoid-lymphocyte" adequately describes the cell.

B. Leukemia, Lymphatic. The bone marrow in the acute and chronic types was identical. However, there was greater immaturity of the lymphocytes in the acute than in the chronic forms. No difficulty was encountered in distinguishing lymphatic leukemia from any other condition simulating it, *i. e.*, infectious mononucleosis, Hodgkin's disease, agranulocytosis, and so on. In no other conditions was the myeloid-lymphoid (My:Ly) ratio so pronounced. Erythrogenesis was depressed also in lymphatic leukemia as shown by the granulocyte-erythroid (G:E) ratio. This finding is of importance since erythrogenesis is increased in agranulocytosis, infectious mononucleosis and Hodgkin's disease.

C. Leukemia, Neutrophilic. This patient, a 69-year-old married woman (seen at the Norwegian Hospital through the courtesy of Dr. Brancato), gave a history of hematuria of 7 days' duration, pain in the right upper quadrant of the abdomen of 4 days' duration and an indolent ulcer of the right leg of several weeks' duration. On physical examination enlarged anterior and posterior cervical nodes were palpated; splenomegaly Grade 2 and hepatomegaly Grade 3 were found. Urinalysis showed albumin Grade 2 and, microscopically, many white blood cells. The report of the peripheral blood was hemoglobin, 95%; red blood cells, 6.6 million; and

white blood cells, 61,000 per c.mm. In the differential were found 87 polys, 8 staff forms, 1 myelocyte and 4 lymphocytes. At this time the clinical impression was pyonephrosis with impending uremia.

TABLE 3.—DISTRIBUTION OF CASES.

I. NORMAL	28
II. PATHOLOGICAL:	
A. <i>Red cell disturbances:</i>	
1. Hyperchromic anemia:	
(a) Pernicious anemia	20
(b) Hemolytic icterus	6
(c) Sickle-cell anemia	5
2. Hypochromic anemia:	
(a) Aplastic anemia	3
(b) Idiopathic achlorhydric anemia	3
(c) Familial telangiectasia	2
3. Polycythemia vera	4
4. Albers-Schönberg disease	1
B. <i>White cell disturbance:</i>	
1. Leukemia, myelogenous:	
(a) Acute	14
(b) Chronic	9
2. Leukemia, lymphatic:	
(a) Acute	6
(b) Chronic	11
3. Leukemia, neutrophilic, leukopenic	1
4. Infectious mononucleosis	8
5. Agranulocytosis	2
6. Hodgkin's disease	22
C. <i>Platelet disturbance:</i>	
1. Purpura hemorrhagica, thrombocytopenic	12
D. <i>Metabolic lipid disturbance:</i>	
1. Gaucher's disease	1
2. Niemann-Pick's disease	2
E. <i>Infections</i>	32
F. <i>Malignancies</i>	29
G. <i>Multiple myeloma</i>	1
H. <i>Malaria</i>	1
I. <i>Liver and gall-bladder diseases</i>	16
J. <i>Miscellaneous</i>	36
Total	275

Study of the bone marrow and concomitant peripheral smear, 1 week after admission, revealed 6 myelocytes, 4 metamyelocytes, 13 staff forms, 75 polys and 2 eosinophils; only occasional normoblasts were seen. The peripheral differential showed 4 myelocytes, 4 metamyelocytes, 12 staff forms, and 80 polys. The platelets were increased and there was slight anisocytosis of the red blood cells. A diagnosis of leukemia could not be entertained at this time, but at autopsy, typical leukemic infiltrations of all the organs were found with the neutrophil as the predominant cell. (Several years ago another case with similar course and autopsy findings was seen.)

D. *Infectious Mononucleosis.* The bone marrow showed a left shift of the white blood cell series with increased rate of red cell activity. The myeloid-lymphoid (My:Ly) ratio was shifted to the

right at times, but never in the proportions seen in lymphatic leukemia. The erythroblast-normoblast (E:N) ratio revealed a defective maturation in these cases. It is problematical at this time to say whether this can be ascribed to lack of anti-anemic principle or some disturbance in its utilization or absorption.

E. *Agranulocytosis*. Here the myeloblasts were the predominant cells in the bone marrow but were not present in profusion. Plasma cells were seen in increased numbers in all the cases. The myeloid-lymphoid (My:Ly) ratio was slightly shifted to the right but never approached leukemic proportions. Erythrogenesis was normal, thus accounting for the lack of anemia.

F. *Hodgkin's Disease*. As far as the red cell mechanism was concerned, the findings were not remarkable since most cases showed only slightly increased activity. On the other hand, it was interesting to note an increase in reticulum cells, a moderate eosinophilia in the bone marrow or peripheral circulation or in both, an increase in megakaryocytes, a peripheral monocytosis, but no Dorothy Reed-Sternberg cells.^{7a,23}

G. *Lymphocytosis*. The cases evaluated were confined to those in which there was a peripheral lymphocytosis of at least 40%. In none of these cases, including infectious mononucleosis, agranulocytosis, aplastic anemia, and so forth, did the myeloid-lymphoid (My:Ly) ratio approach that seen in lymphatic leukemia. It appears therefore, that the My:Ly ratio is a *sine qua non* in differentiating lymphatic leukemia from conditions which simulate it.

DISEASES OF THE ERYTHROPOIETIC MECHANISM. A. *Defective "Ferrization."* Interference with the formation, maturation or destruction of the red blood cells will produce certain definite bone marrow pictures. The increase in the red cell elements observed in these conditions is a compensatory one. The formation of hemoglobin is intimately related with the ingestion, absorption and utilization of iron. Any iron defect will be mirrored by the presence of iron-poor red cells. There is an attempt to make up in number what it fails to do in quality. Thus, in Witt's hypochromic anemia, infections, malignancy, hemorrhage, and so forth, one sees in the bone marrow an increased erythropoiesis.

In spite of the increased bone marrow erythrogenesis, there is a peripheral anemia. This can be accounted for on the basis of arrest in delivery, hemorrhage and destruction due to hemolysis, infection and poisons.

B. *Defective Maturation*. The increase in bone marrow erythrogenesis alone is not to be compared with that seen when there is a concomitant maturative defect of the red cells. In the former the G:E ratio and the E:N ratio are about 70:30 and 15:85, respectively. In the latter the G:E and the E:N ratios would be 50:50 and 70:30 respectively. In the former the color index, therefore, is low while in the latter it is high. The bone marrow picture

TABLE 4.—HEMATOPOIETIC PERCENTAGES AND RATIOS IN THE BONE MARROWS OF VARIOUS CONDITIONS.

	Normal.	P. A.	Poly. vera.	Hemoly. icterus.	Hypo. anemia.	Aplastic anemia.	Infection.	Malignancy.	Chronic myel. leukemia.	Acute myel. leukemia.	Agranulocytosis.	Lymph. leukemia.	Infectious mononucleosis.	Lymphocytosis.	Hodgkin's disease.	Purpura hemorrh.
Myeloblast	2	0	2	11	9	10	5	16	0	85	88	3	0	3	4	1
Myelocyte	32	20	40	22	23	40	45	26	40	10	12	40	40	36	20	33
Eos. myelocyte	1	0	0	2	4	2	0	2	0	1	0	2	5	0	6	1
Metamyelocyte	8	15	7	6	9	10	13	20	10	1	0	16	15	15	0	12
Staff forms	10	20	17	26	11	4	20	18	25	1	0	20	20	24	23	16
Segmented forms	46	42	32	26	41	27	16	18	25	1	0	15	20	15	38	34
Eosinophils	1	3	2	7	3	7	1	0	0	1	0	3	0	7	9	3
Ratios: N:S:S	55:45	55:45	60:34	67:33	56:44	55:45	83:17	82:18	75:25	98:2	99:1	..	80:20	78:22	53:47	63:37
Delivery	N	N	N	+	+	+	+	+	N	+	0	..	N	+	+	+
G:E	85:15	40:60	67:33	15:85	74:26	96:4	94:6	65:35	95:5	95:5	30:70	..	70:30	80:20	85:15	90:10
E:N	15:85	70:30	64:36	30:70	30:70	30:70	30:70	50:50	40:60	20:80	50:50	20:80	40:60	10:90	10:90	30:70
My:Ly	90:10	90:10	95:5	95:5	82:18	85:15	95:5	95:5	98:2	95:5	60:40	10:90	90:10	90:10	90:10	88:12
My:Plasma cell	98:2	65:35	88:12	95:5	95:5	98:2	..	98:2
Megakaryocytes	..	+	+	N	N	+	N	N	N	0	+	0	+	+	+	+
Reticulum cells	+	+	+
Number of cases	28	20	4	6	8	3	32	29	9	14	2	17	8	31	22	12

in the hyperchromic anemias is one of defective maturation with marked marrow erythrocytogenesis, whereas in the hypochromic anemias it is one of deficient "ferrization" with mild erythrocytogenesis.

C. *Defective Destruction.* The cases of idiopathic polycythemia vera observed in this study did not display the extensive bone marrow erythrocytogenesis²³ that one expected to find in these conditions.

The erythrocytogenic activity of the bone marrow did not appear to be increased. Such increases, in our experience, were only a compensatory mechanism in an attempt to overcome peripheral anemia. Since the latter was not encountered in polycythemia vera, increased bone marrow erythrocytogenesis was not necessary.

It is questionable whether the production of polycythemia can be postulated on increased red cell production alone. This certainly is not borne out by this study. On the other hand, it is possible that there is underdestruction of the red blood cells, associated with decreased hemolytic activity on the part of the spleen, *i. e.*, hyposplenism.

D. *Increased Production of the Red Blood Cells.* On the other hand, symptomatic polyglobulia secondary to respiratory and cardiac changes associated with anoxic states is the fact a "true" polycythemia, in the sense that here one deals with an increased production because of cerebral stimulation. In these cases there is usually no splenomegaly.

HYPOCHROMIC ANEMIAS. Included in these cases were aplastic anemia of the idiopathic type; another due to benzol poisoning; cases of idiopathic hypochromic anemia and familial telangiectasia and a case of Albers-Schönberg's disease. There was an increased bone marrow erythrocytogenesis in all these cases except in the first two where there was a definite paucity of the erythroblastic elements. In the first (Case 182), the interesting feature was the absence of changes in the leukogenetic and thrombocytic elements. The white blood cells numbered 8000, the platelets were normal, but the hemoglobin was less than 20% and the red blood cell count was 700,000. This was a true selective action upon the red blood cells. Brancato has called this condition "Anerythroplastic Anemia." This was a 7-year-old girl with pallor since birth. She had received many transfusions with no significant improvement. In the second case, the prominent findings were toxic degeneration of the granulocytic elements accompanied by a marked increase in plasma cells. Multiple myeloma was difficult to exclude in this case. The erythrocytic and thrombocytic elements were markedly diminished. This was a true panmyelophthisis, due to benzol poisoning.

HYPERCHROMIC ANEMIAS. In this category were cases of pernicious anemia, treated and untreated, and other hyperchromias which did not fit either clinically or hematologically into the definite pernicious anemia group. Such cases were seen in pregnancy, infection, hyperthyroidism, achlorhydric anemia, and so forth. Then there were the hyperchromias revealed in hemolytic anemias, sickle cell

anemia, Cooley's anemia, erythroblastic fetalis, and so forth. In all these cases there was a common denominator, *i. e.*, defective maturation of the red blood cells. Megaloblasts differentiated into the normoblasts but poorly and eventually into the normocyte. There was an arrest predominantly at the macrocytic phase. In the bone marrow this was easily observed in the preponderance of the early erythroid elements that accounted for an increased E:N ratio with a consequent hyperchromia or high color index.

It may not be amiss to review briefly the *modus operandi* of defective erythrocytic maturation, in relation to liver and gastric dysfunction and other conditions. In the first place, structural disease or dysfunction in the liver may disturb "the anti-anemic factor" (Whipple²⁴). A corollary to this is the possible interference with the "intrinsic factor" (Castle^{4,5,22}) in pathologic conditions of the stomach. By the same token, interference with absorption of the anti-anemic substance in the intestines so that it does not reach the liver may influence changes in the E:N ratio.

Thus it may be seen how gastric⁴ or hepatic disturbances^{19,24} may approximate a set of conditions seen in pernicious anemia and other hyperchromias.^{7a,17} Gastric anacidity especially has been associated with a similar maturative defect.^{4,12} Gastric motility also plays a rather significant part in the function and efficiency of the bone marrow (Barron^{1,2} "It suggests," corroborating Doan's^{7b} statement, "a motor factor in addition to the secretory deficiencies as part of the mechanism which may condition this phenomenon of blood cell maturation."

In brief, the lack of anti-anemic substance may be evident in other conditions, where interference with its ingestion, absorption, storage or utilization is marked. Thus cirrhosis (storage), gastric malignancy (storage or formation of anti-anemic substance) are all capable of producing changes in the E:N ratio with resulting pernicious anemia-like pictures.

In the bone marrow, all hyperchromias are essentially alike except for certain peculiarities. In pernicious anemia aside from the change in the E:N ratio there is marked macrocytosis, "ripe" polys, presence of occasional megaloblasts, and in the untreated cases, at times, a shift to the right of the white blood cells. In the treated cases, there is a shift of the E:N ratio to the right and the N.S:S ratio to the left, producing eventually a low or normal color index with a slight leukocytosis. In hemolytic icterus the picture is identical to that seen in pernicious anemia except for the presence of "microcytosis," and the macronormoblastic erythrogenesis.¹³ There is a greater left leukogenesis in these cases than those seen in true pernicious anemia, thus accounting for the leukemoid reaction sometimes observed in these cases. A remarkable reversal of the E:N ratio was accomplished by splenectomy in 2 cases. In Cooley's anemia, sickle cell anemia and erythroblastosis fetalis, the

bone marrow findings are identical. The diagnosis must rely on the clinical features, *i. e.*, in Cooley's anemia, the mongoloid facies and peculiar roentgenographic findings in the skull and other bones; in sickle cell anemia sickle cells are found in the bone marrow and peripheral stream.

DISORDERS OF THE PLATELET MECHANISM. Observations on this mechanism are based on 12 cases of purpura hemorrhagica. The outstanding finding in all these cases was the presence of an increase in the megakaryocytes in the bone marrow. The thrombocytopenia in these cases is probably due to thrombocytolysis on the part of the spleen. Support of this hypothesis in the study comes from the fact that after splenectomy the megakaryocytes are markedly reduced in the bone marrow. In addition, at the same time there occurs a peripheral thrombocytosis.

Aside from the above findings, one was impressed by the increased bone marrow erythropoiesis. This was probably a compensatory mechanism consequent to bleeding. Another interesting feature was the presence of a definite defect of the red cell maturation. This may be due to interference with storage of anti-anemic substance. This also may be due to gastric, liver, intestinal or renal lesions probably as a result of frequent hemorrhages. Eosinophilia was also prominent in most of the cases. The latter was probably due to absorption of blood on the basis of foreign protein sensitization. This conclusion is strengthened by the fact that in 3 cases of uncomplicated hemorrhage eosinophilia was a prominent factor. Thrombocytopenia due to causes other than idiopathic purpura were not associated with a bone marrow megakaryocytosis. This was especially true in acute leukemia and aplastic anemia. The bone marrow megakaryocytosis is in all probability a compensatory mechanism predicated on a hypersplenism for thrombocytes. The bone marrow in this case tries to overcome the deficiency with an overproduction. Normally there are very few megakaryocytes to be seen in the bone marrow. The peripheral thrombocytopenia is produced by defective delivery or destruction of the parent megakaryocytes. The megakaryocytes in idiopathic purpura apparently were no different from the megakaryocytes normally encountered in the bone marrow.

Hodgkin's disease and some malignancies produced comparable increases in megakaryocytosis.

DISEASES OF LIPOID METABOLISM. Here were included 2 cases of Niemann-Pick's disease and a case of Gaucher's disease (more than 10 Gaucher cells per 100 white blood cells).²² There were no remarkable changes in the bone marrow in these cases. Erythropoiesis was slightly increased in these cases in both conditions, but the accompanying anemia was in all probability due to the compression of the erythroblastic elements by the invading histiocytic elements. A description of these cells has already been given. Leukopoiesis was slightly increased in Niemann-Pick's disease and dimin-

ished in Gaucher's disease. This may explain the leukocytosis in the former and the leukopenia in the latter.

INFECTIONS. In the majority of the cases there was a significant acceleration of leukogenesis. In over half of the cases the metamyelocytes showed definite increases, in addition to the larger number of staff forms. An important differential point from chronic myeloid leukemia from the leukemoid reaction of infection was the presence of increased erythrocytogenesis in the latter, while this was diminished in the former. In infections there was also a defective maturation of the red blood cells.

Another important aid in distinguishing infections or other leukemoid reactions from chronic leukemic myelosis was the prominence of azurophilia in the myelocytic elements of the latter. This was due to the increase of premyelocytes. It was an easy matter to distinguish acute infections from acute leukemias, on the basis of the distinctive myeloblastosis of the bone marrow and the peripheral stream in the latter condition. This was further aided by the diminution of the megakaryocytes in the acute leukemias. The defective maturation of the red cells in both conditions may be postulated on interference with storage, absorption or utilization of anti-anemic substance. In infections this was based on inflammatory lesions, in the latter on infiltrative lesions.

MALIGNANCY. Here the changes were identical with those seen in infections. This was an important factor in the diagnosis of malignancy. In other words, if the bone marrow shows evidence of a leukemoid reaction, malignancy may be suspected if infection, hemorrhage or toxemia can be ruled out on clinical grounds. An infection to give rise to a leukemoid picture of the degree observed in cases of malignancy usually is associated with a moderate rise in temperature (102° to 103°).¹⁴

LIVER AND GALL-BLADDER DISEASES. The changes in the white and red cell elements of the bone marrow were similar to those seen in any leukemoid reaction, *viz.*, infection, malignancy and hemorrhage. The erythroid maturative defect in these cases may be due to the compromising of liver structure, thus interfering with storage and utilization of anti-anemic substance. In turn, this yields an increased E:N ratio and a resulting high color index. Interesting is the finding of eosinophilia in 6 cases. This may be due to the destruction of liver parenchyma with consequent reabsorption of non-specific protein.

Bone marrow study becomes a possible means of aiding in the diagnosis of disturbed liver function, produced by such conditions as inflammation, toxemia, hemorrhages, cysts, angiomas or infiltrative lesions due to leukemia, Hodgkin's disease or malignancy.

In fact, the E:N ratio or high color index may serve as a veritable liver function test in a motley group of conditions. This may yield information even before clinical manifestations such as enlarged

TABLE 5.—AVERAGE PERCENTILE DISTRIBUTION OF LEUKOPOIETIC CELLS IN THE BONE MARROW.

	Authors.	Arinkin.	Barta.	Dameshek.	Escudévo and Varella.	Holmes and Braun.	Custer and Krumbhaar. ⁶	Nordenson.
	Range.	Range.	Range.	Range.	Range.			Range.
Myeloblasts . .	2 (0-3)	1.7 (1-2.4) 3.0	2.5 (2-3) 3.0	5.5 8.4	2.4 4.8	0.6 0.8	2.9 (0.25-55) 3.5
Promyelocytes	1.9 (1-2.8) 3.1	7 (6-7) 7.5	1.5 (1-2) 3.75	8.4 14.6	9.0 15.4	4.8 (1.25-8.25) 5.5
Myelocytes . .	32 (20-35)	5.1 (4.5-8.6) 8.5	41 (40-42) 48.0	20.0 (15-25) 50.0	20.5 24.0	7.0 15.0	34.6 53.7	11.2 (4.25-18) 14.5
Metamyelocytes .	8 (5-10)	2.4 (1.4-3.4) 4.0	21 (20-22) 24.0	15.0 (10-20) 37.5	27.4 43.0	6.7 14.4	14.6 22.4	27.3 (12.5-42) 34.25
Staff forms . .	11 (5-15)	7 (6-8) 7.5	14.0 29.5	6.5 (2.25-10.75) 8.0
Segmented forms .	46 (40-50)	48 (41-55) 81.4	9 (8-10) 10.0	1.5 (1-2) 3.75	17.4 36.3	3.0 4.5	25 (14.25-35) 34.25
Eosinophils . .	1 (1-2)	2.0 (1-3) 5.0	2.0 3.2

	Rohr.	Rosenthal.	Schilling and Benzlter.	Segerdahl.	Schulten.	Tempka and Braun.	Weiner and Kaznelson.	Young and Osgood.
Myeloblasts . .	1.3 1.5	1.6 (0.4-5.0) 1.8	1.3 2.6	6.5 (1-12) 10.7	5.8 (4.7-7.0) 8.25	4.6 6.0	0.4 (0-1.2) 0.8
Promyelocytes . .	9.5 11.4	1.4 2.8	4.5 (1-8) 7.4	5.3 (3.75-6.8) 6.75	5.0 6.5	1.5 (0-3.8) 3.0
Myelocytes . .	6.6 7.9	21.5 (12-32) 24.4	41 (35-47) 40.6	16 32.2	7.0 (4-10) 11.7	13 (12.7-13.3) 16.0	19.4 27.0	1.7 (0-4.0) 3.4
Metamyelocytes .	8 9.6	45 (34-56) 44.5	14.0 (1-27) 23.4	15.4 (14.3-16.5) 20.5	15.7 21.0	0.8 (0-2.6) 1.6
Staff forms . .	41 49.2	30.2 (12-40) 34.35	0.5 (0-1) 0.5	10 20.1	19.5 (17-22) 25.5	6.3 8.5	7.4 (1.8-9.8) 15.0
Segmented forms .	17 20.4	34.0 (20-50) 38.45	14.5 (7-22) 14.4	21 42.3	28.0 (1-55) 46.8	18.0 (16-20) 23.0	22.3 31.0	24.1 (15.8-33) 48.5
Eosinophils	0.94 (0.2-2.8) 1.03	13.3 (7.4-25.2) 26.9
								0.4 (0-1.0) 0.8

Figures in italics: Averages recalculated so that the sum of the granulocytic cells equals 100.

liver, jaundice, pruritus have made their appearance and icterus index, Van den Bergh test, and examinations for bile in urine and stools have been done. Cases of cholecystitis, a case of hypertrophic biliary cirrhosis (Case 45), a case of liver abscess (Case 246), and a case of hepato-splenomegaly of undetermined origin (Case 168), did not show an increased E:N ratio or high color index and therefore liver damage could not be postulated.

MISCELLANEOUS CONDITIONS. *Multiple Myeloma* (1 case). Leukogenesis was normal, erythrogenesis was moderately increased with a moderate defect in maturation of the red blood cells. The outstanding feature was an increase in plasma cells. Bence-Jones protein was present in the urine. The patient was a 40-year-old woman who complained of weakness and pain in the legs and back for 6 weeks. When first seen her hemoglobin was 35%, the red blood cells were 2,000,000, the white blood cells 30,000 and the platelets 70,000. In the peripheral smear 10% plasma cells were counted.

Arthritis. There were no significant findings except for some increase in leukogenesis with slight erythrogenesis associated with a defect in the maturation of the red blood cells.

Malaria. Plasmodia were seen both in the bone marrow and the peripheral red blood cells but were definitely more numerous in the red blood cells of the bone marrow.^{3,9,16,21,23}

There was a group from which no significant conclusions could be drawn. These were cases of: tuberculosis of the lung with spinal metastases, intestinal parasites, gold poisoning, diabetes with coronary occlusion, scleroderma associated with Raynaud's disease, Kaposi sarcoma, calcinosis universalis, neuroderma, eczema, bronchial asthma with hyperthyroidism, erythema nodosum, pemphigus, multiple melanoma, Winckel's disease and rheumatic heart disease.

Comment. Of 275 cases studied, bone marrow aspirations were of great diagnostic aid in 47 cases in which clinical signs and symptoms and routine blood examinations failed to be of assistance. These cases were Hodgkin's disease (8), carcinoma (15), infections (3), anemia of pregnancy (1), pernicious anemia (8), anerythroplastic anemia (1), infectious mononucleosis (1), Gaucher's disease (1), aplastic anemia (1), both varieties of leukemia (7), and atrophic cirrhosis of liver (1).

However, diagnosis was not the only purpose for which the study of the bone marrow was utilized. There were definite observations made of various mechanisms that concerned the blood dyscrasias and other conditions such as malignancies, infections and infiltration of the bone marrow.

In discussing these conditions seriatim, leukogenesis is first considered. Observations of leukogenesis in this series confirmed the "shift to the left" theory of Arneith and Schilling as far as the bone marrow was concerned. The most marked left shifts were in the acute myeloid leukemias, then in the chronic myeloid leukemias, in agranulocytosis, in infections and in malignancies. Slighter degrees

of left shift were found in treated pernicious anemia, in a case of Niemann-Pick's disease, Cooley's anemia, liver and gall-bladder diseases and infectious mononucleosis. Diseases in which left shift was negligible or shifted to the right were cases of polycythemia vera, purpura hemorrhagica, untreated cases of pernicious anemia, pernicious-like anemias, and certain cases of arthritis and Hodgkin's disease.

It is instructive to compare the almost identical bone marrow pictures that obtain in acute myeloses and agranulocytosis. In this study it was evident that there was a more increased tempo of delivery in the leukemias as compared to agranulocytosis. It appeared, therefore, that the pathogenesis in agranulocytosis was an arrest in delivery in addition to a marked left shift, whereas in acute myelosis the granulocytic delivery was not impeded. A point of marked value in the differential of these two conditions is the unimpaired erythroid activity in agranulocytosis while in acute myelosis it is definitely depressed.

The outstanding differential factor in separating chronic myeloid leukemias from the leukemoid reactions caused by infections, hemorrhages or malignancy and toxemias is the N:E and G:N ratios. The former is markedly depressed in chronic myeloid leukemias and the latter not as marked as that occasioned by the leukemoid reactions.

The most characteristic pathognomonic finding in this study was the unequivocal lymphatic infiltration of the bone marrow seen in lymphatic leukemia. This was made quite prominent by using the myeloid-lymphoid (My:Ly) ratio. Lymphocytoses of high degree and infectious mononucleosis could be differentiated very easily by means of this ratio. The latter conditions never gave rise to marked infiltration of the bone marrow with lymphocytes.

As for erythropoiesis, one was able to determine the state of erythropoietic activity by the granulocyte-erythroid (:E) ratio. We found this increased in many of our cases. It is necessary to point out that in 85 cases where there was moderate erythropoiesis in the bone marrow, there was no evidence in the periphery of such activity in 36 cases. This would lead one to believe that the bone marrow serves to acquaint us with conditions concerning erythropoietic activity which cannot otherwise be determined in routine peripheral blood examination.

Erythropoiesis was most marked in the hemolytic anemias, hemolytic icterus, sickle-cell anemia, Cooley's anemia, Niemann-Pick's disease, occasional treated and untreated cases of pernicious anemia, a few cases of Hodgkin's disease; it was slightly increased in malignancies and showed a similar picture in infections. Increased erythropoietic activity was conspicuous by its absence in leukemias. It is interesting to again refer to the meager increase in erythropoiesis in polycythemia vera. One may see, therefore, the bone marrow is not alone responsible for the peripheral polycythemia. It is necessary to postulate a longer life of the red blood cells most of which are sequestered in the spleen and in other reservoirs.

If it is true that the lesions of polycythemia vera are not primarily confined to the bone marrow, then it would seem that treatment directed against bone marrow erythropoiesis is futile. Thus Roentgen ray becomes of questionable value when used in this way.

A valuable diagnostic differential finding is that erythropoiesis is diminished or absent in leukemias and is unimpaired both in agranulocytosis and infectious mononucleosis.

We found a certain parallelism between erythropoiesis and erythrocytic maturative defect in the bone marrow. This was exceedingly striking in sickle-cell anemia, in hemolytic icterus and to a lesser extent in untreated cases of pernicious anemia, and to a still lesser degree in infections and malignancies. The most marked and constant defects in maturation were found in pernicious anemia. This was not true of pernicious-like anemias. Here the defects were of lesser moment. Hemolytic icterus, Cooley's anemia and sickle-cell anemia were slightly less prominent in their maturative defect. There were slighter degrees of defect in purpura hemorrhagica, infections and malignancies. In chronic myelogenous leukemia the maturative defect was not constant.

As was pointed out previously, the color index as obtained by peripheral study has the same significance as the erythroblastic maturative defect and may therefore be used in the same way. Here one finds an instance where a study of the bone marrow has brought significance to a routine procedure. One may state that a high color index is of great diagnostic importance in postulating liver damage, gastric defect, carcinoma of the stomach, malignancy, and infection in selected cases.

One of the surprising findings, almost similar to that experienced in polycythemia vera was the presence of an increased number of megakaryocytes in the cases of purpura hemorrhagica, even exceeding in number those found in Hodgkin's disease. This would rather militate against the hypothesis of Frank⁸ who postulated that "an essential thrombocytopenia is secondary to an inhibitory action of the spleen on the bone marrow." Our evidence favors the conception of Kaznelson¹¹ who performed the first splenectomy for thrombocytopenic purpura, basing his theory on the hypothesis of the destructive activity of this organ for platelets.

From a study of this material we uncovered certain criteria that proved to be of great diagnostic aid in the study of various conditions. In carcinoma of the stomach, for instance, there was always a maturative defect of the red blood cells. In other malignancies the N:S:S and G:E ratios were frequently increased. In infections there was a constant increase in left shift involving the metamyelocytes and the staff forms. The N:S:S and G:N ratios were also shifted to the left. Since the same is true of malignancies, the absence of fever associated with the blood picture would favor malignancy and rule out infection.

Certain other diagnoses, one felt, could not accurately be made except by means of the bone marrow. We refer to the finding of Gaucher cells, Niemann-Pick cells and plasma cells. The presence of an increase in plasma cells would speak for a multiple myeloma if corroborative clinical evidence is available, since the latter may be present in certain aplastic or myelophthisic anemias.

In Hodgkin's disease there was a poor left shift or a shift to the right of the white blood cells associated with an increase in the eosinophilic elements in the bone marrow accompanied by an increase of the reticulum cells. The megakaryocytes were always increased. Erythrogenesis was always active. The E:N ratio was normal or slightly shifted to the left. Eosinophilia and monocytosis in the peripheral circulation was valuable, but when absent did not rule out Hodgkin's disease.

Conclusions. 1. A study was made of 275 cases with sternal bone marrow aspiration.

2. Bone marrow ratios were utilized in evaluating: *a*, Leukogenesis; *b*, erythrogenesis; *c*, erythrocytic maturative defect; *d*, infiltration of bone marrow by lymphocytic, plasma, reticulum and malignant cells.

3. Bone marrow aspirations proved valuable in the diagnosis of gastric dysfunction and gastro-intestinal, liver, and renal disease.

4. This study revealed a close relationship between the erythrocytic maturative defect and color index.

5. Criteria for the diagnosis of blood dyscrasias including pernicious anemia, Hodgkin's disease, leukemia, agranulocytosis, infectious mononucleosis, polycythemia vera, infections and malignancies are suggested.

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AURICULAR STANDSTILL.

ITS OCCURRENCE AND SIGNIFICANCE.

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AURICULAR standstill is a disturbance of cardiac rhythm which has long been recognized in experimental animals but which has been reported only rarely in clinical cases. In this disorder, the auricles cease to beat, the electrocardiogram showing no evidence of auricular activity in any of the standard leads. The ventricles continue to beat with an independent, regular rhythm, the ventricular complexes in the electrocardiogram having the conformation of beats of supra-ventricular origin. Furthermore, there is no evidence that the auriculo-ventricular node is inducing auricular activity.

As long ago as 1897, Cushny³ produced this condition in dogs with toxic doses of digitalis. Later, Lewis and his co-workers⁷ observed it in dogs given large doses of strophanthin. Auricular standstill has been induced in dogs with quinidine by Haskell,⁴ Korns⁵ and Lewis, *et al.*⁸ Employing both isolated rabbits' hearts and fetal hearts, Boden and Neukirch¹ demonstrated auricular standstill by the progressively increasing action of quinidine, restoring the normal rhythm by subsequent perfusion with Tyrode's solution. Lewis, White and Meakins⁹ described auricular standstill in cats in the late stages of simple asphyxia and also, when, during the early stages of asphyxia, cold was applied to the sino-auricular node. More recently, Borman and McMillan² have repeated this effect in a dog by cooling the sino-auricular node area after radon had been implanted in that same region some time previously.

A review of the literature^{6,10a,b,11-15} has revealed 8 clinical cases in which the evidence for auricular standstill is definite and 4 in which it must be considered a questionable diagnosis because of inadequate information supplied. Of this number, 4 had received digitalis and in 5 of them quinidine had been administered. One had subacute bacterial endocarditis with many small areas of necrosis in His' bundle;^{10a} another had rheumatic pancarditis.^{10b} In these latter two instances and a third described by Lewis,⁶ no mention of drug therapy is made. Polygraphic tracings reproduced in the publications of Lewis⁶ and White¹² prove that in auricular standstill there is complete mechanical as well as electrical inactivity. In 1929, in their discussion of 2 cases appearing with quinidine, Wolff and White¹⁵ pointed out the possibility of standstill of the whole heart due to depression of

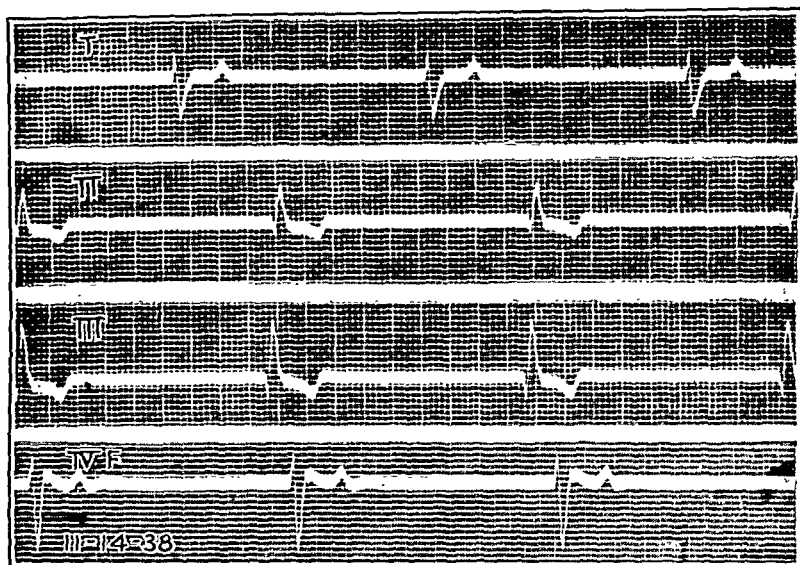
the ventricular as well as the auricular pacemaker, as the cause of sudden death during the use of that drug.

Clinical Material and Findings. A review of the case records and electrocardiograms at this hospital in the period from May 1929, to January, 1939, has yielded 8 cases in which we believe a definite diagnosis of auricular standstill can be made. In addition, there are 4 cases in which it is a probable diagnosis, though lack of control electrocardiograms before or after the period of standstill make a certain diagnosis impossible. In our experience the differentiation of auricular standstill and nodal rhythm is often difficult. We have excluded all such doubtful instances of this disorder. Essential details are summarized in Table 1.

TABLE 1.—CASES OF AURICULAR STANDSTILL FROM MAY, 1929, TO JANUARY, 1939.

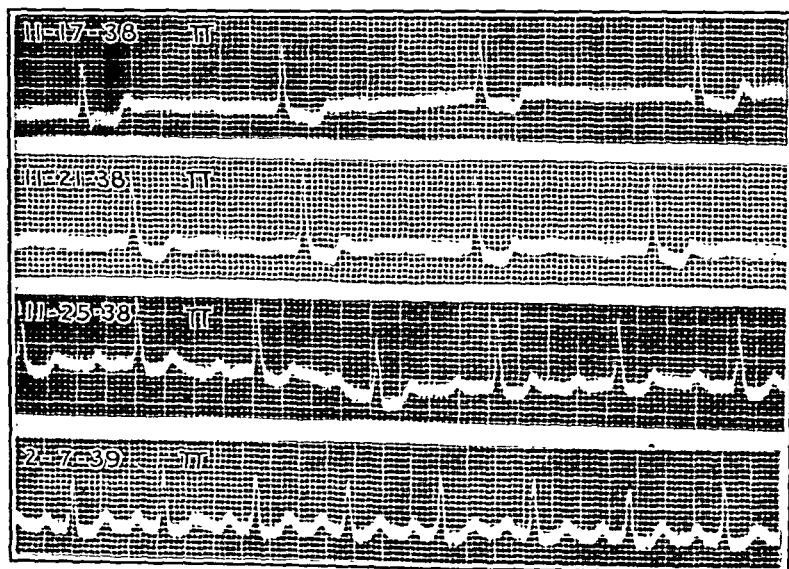
	Definite diagnosis.	Probable diagnosis.
Number of cases	8	4
Age:		
Range	46-79	16-52
Average	67	42
Sex:		
Males	6	4
Females	2	0
Previous rheumatic fever	0	0
Positive Wassermann	1	3
Hypertension	5	1
Type of heart disease:		
Valvular:		
Syphilitic	1	3
Rheumatic	1	0
Coronary arteriosclerosis	6	0
Syphilitic aortitis	0	3
None	0	1
Cardiac enlargement:		
None	0	1
Moderate	3	0
Marked	3	3
Very marked	2	0
Congestive failure	8	3
Outcome:		
Death in hospital	2	3
Death at home in short time	2	0
Known living	2	1
Lost	2	0
Digitalis:		
Small or usual doses	1	1
Large doses	6	2
Evidences of toxicity	5	3
Quinidine	2	0
Return of auricular activity	5	1
Other evidences of defective conduction mechanism or site of impulse formation	6	3

The analysis of these cases reveals several interesting points. Most of them were in the fifth, sixth and seventh decades of life. All but one had serious heart disease and evidence of moderate to severe congestive heart failure. The single exception was a 16-year-old boy who had diabetes mellitus and appendicitis, the electrocardiogram being taken because of an irregular cardiac rhythm



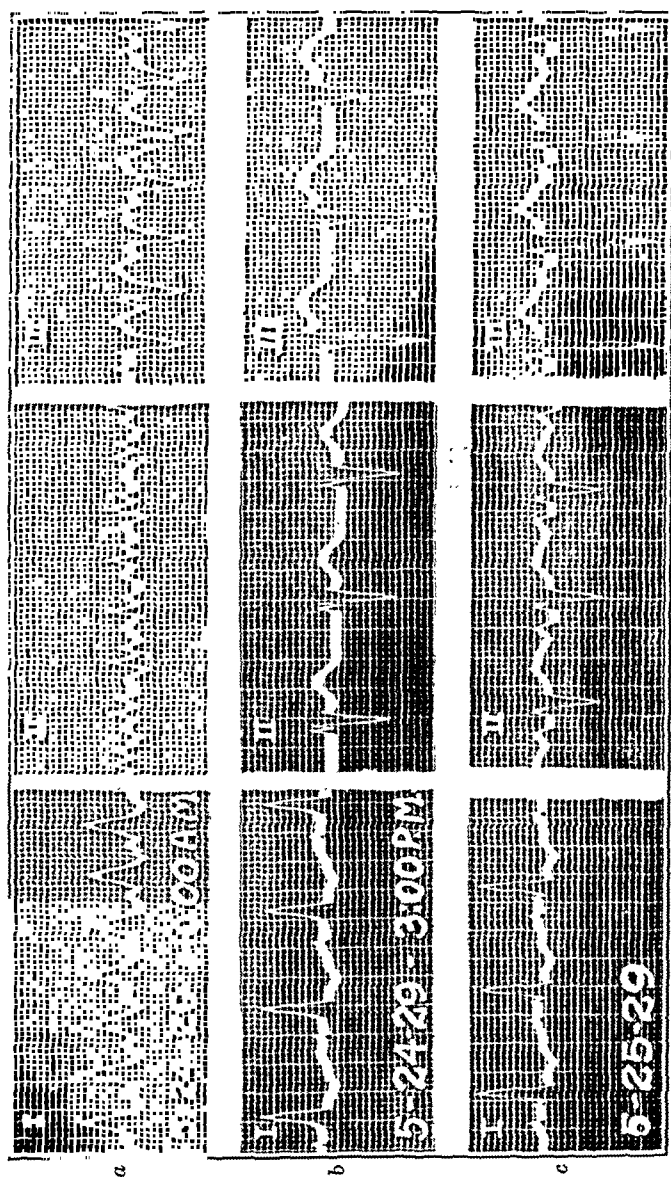
J. J. McI., No. 53,908.

FIG. 1.—Case 1, Nov. 14, 1938. Complete standstill of auricles. Ventricular rate 33.3 per min. Patient had had excessive digitalis.



J. J. McI., No. 53,908.

FIG. 2.—Case 1. Return of auricular activity on Nov. 25, 1938. *P-R* interval on Nov. 25, 1938, 0.28 sec. *P-R* interval on Feb. 7, 1939, 0.16 sec. Note gradual return of normal mechanism after omitting digitalis.



R.W., Private Case.

FIG. 3.—Case 2. Upper tracings show paroxysmal ventricular tachycardia with ventricular rate of 169.0. Middle set shows auricular standstill in Leads II and III. Lower set shows return of auricular activity and left bundle branch block. Patient had received a single dose of 1 G. of quinidine sulphate at 11:30 A.M. on May 24, 1929.

hospital day, after having been quite comfortable since admission, the patient's respirations suddenly ceased, he became extremely cyanotic and his radial pulse could not be felt. With artificial resuscitation, adrenalin hydrochloride 1.0 cc. 1 : 1000 solution subcutaneously, and coramine (Ciba) 1.5 cc. intramuscularly, his respirations and heart beat reappeared within a few minutes, the cardiac rhythm being the same as on admission. An electrocardiogram taken $\frac{1}{2}$ hour after this episode was essentially as on admission. Ephedrine sulphate 0.025 G. every 4 hours for 2 days and 3 times daily thereafter for 6 days together with occasional doses of adrenalin subcutaneously had no demonstrable effect on the cardiac rhythm or the electrocardiogram. Repeated doses of atropine sulphate 0.0005 G. hypodermically were also without effect. As the digitalis was eliminated from the body the cardiac rate became progressively more rapid and the auricular waves returned in the electrocardiograms together with a progressively decreasing *P-R* interval (Fig. 2). His subsequent course was characterized by gradual improvement and was uneventful except for a transient period of visual and auditory hallucinations. At the time of his discharge on his 24th hospital day he was ambulatory without evidence of congestive failure. When seen subsequently on Feb. 7, 1939, he had continued well without medication of any kind and was up and about freely. Physical examination showed no evidence of congestive failure.

CASE 2.—R. W., diagnoses: Coronary artery sclerosis, coronary thrombosis (old), paroxysmal ventricular tachycardia, left bundle branch block, auricular standstill appearing with quinidine. A male, aged 68, entered the hospital May 23, 1929, complaining of weakness and dyspnea. *Present Illness:* The patient had been well until April, 1927, when he suffered an attack of acute coronary thrombosis with satisfactory clinical recovery, being able to return to work after 3 months. In January, 1929, he had an attack of paroxysmal ventricular tachycardia from which he recovered spontaneously after 24 hours. On May 21, 1929, he suddenly became momentarily unconscious and subsequently was found to have a rapid, regular heart action with a rate of 190. Vagal stimulation induced no change in the heart rate. He grew progressively more weak and dyspneic, developed Cheyne-Stokes respirations and shortly before admission appeared to be in shock. *Physical Examination.* On admission, the patient was found to be a fairly well developed, aged male, in desperate condition, coughing with occasional production of blood-tinged sputum. $T-99.5^{\circ}$, $P-190$, $R-24$. Heart apex impulse diffuse. Evidence of moderate enlargement to percussion. Rate extremely rapid, rhythm regular with accentuation of every seventh or eighth beat. No murmurs heard. B.P., 110/70. Lung fields showed râles at both bases posteriorly. Liver moderately enlarged. Both legs revealed many varicose veins.

Laboratory Examinations. Leukocytosis of 25,900 on admission with progressive fall to normal during his hospital course. Sputum with Type IV pneumococci. Remainder of studies not significant. Roentgen-ray of the chest revealed findings consistent with an extensive bronchopneumonic process. *Clinical Course.* The electrocardiogram on admission (Fig. 3a) confirmed the clinical impression of paroxysmal ventricular tachycardia. Prior to admission he had received a total of 1.8 G. of quinidine sulphate in 4 divided doses without effect. He was given 0.8 G. of quinidine shortly after his entrance and the heart rate slowed to 164. On the second hospital day he received a single dose of 1.0 G. of quinidine and $3\frac{1}{2}$ hours later the rate was 80. An electrocardiogram (Fig. 3b) showed auricular standstill. This was transient inasmuch as the *P*-waves reappeared in Lead I after they had been absent in a portion of the curve not available for reproduction here. Quinidine was continued in doses of 0.3 G. 3 times daily for 2 days and on this régime the auricular activity returned (Fig. 3c). The patient continued

to be febrile, somewhat irrational and severely ill for 7 days after which time there was progressive rapid improvement. He was discharged on the 19th hospital day with advice to spend another month in bed. At the time of discharge the heart rate was 85 and the rhythm normal.

Conclusions. This series of 8 cases of auricular standstill (with 4 other probable cases) confirms the belief that digitalis or quinidine intoxication are the most common causes of auricular standstill. When there is electrocardiographic evidence of its presence, the nature and dosages of the drugs being given the patient should be investigated and adjusted. This group of cases further indicates that the disorder tends to occur more commonly in older patients who are in congestive failure from serious heart disease. Particularly in view of Case 1, whose pulse and respirations were seen to cease for a short time and in whom auricular standstill was known to exist both before and immediately after this event, we believe it is well to reemphasize the fact, pointed out by Wolff and White,¹⁵ that the mechanism responsible for this cardiac disorder may be closely related to some instances of sudden death during digitalis or quinidine therapy. Finally, it would appear from these cases that auricular standstill resulting from quinidine tends to be far more transient than that due to digitalis.

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STUDIES ON IONTOPHORESIS.

I. EXPERIMENTAL STUDIES ON THE CAUSES AND PREVENTION OF IONTOPHORETIC BURNS.

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AND

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THE nature and causes of burns occasionally following an iontophoretic application are not well understood. These burns, which tend to heal slowly (Cumberbatch,⁶ Kovacs¹³), may occur without

the patient's awareness and constitute one of the principal objections against general application of this method of drug administration, although its advantages in certain conditions are so pronounced that its use has been steadily increasing (Abel,¹ Bredall,² Cohn and Benson,⁴ Coulter,⁵ Doane and Scheinberg,⁷ Duryee and Wright,⁸ Jacoby,¹² Loman *et al.*,¹⁵ Murphy,¹⁶ Saylor *et al.*¹⁹). A study of the causes of iontophoretic burns and means for their prevention therefore seemed timely.

With a galvanic current of sufficient intensity, iontophoretic burns can regularly be produced in animals. Fifteen milliamperes, flowing through an electrode area of 10 sq. cm., produces burns in a rabbit in about 30 minutes. In other animals the time and intensity of current is different, but within the same species the individual sensitivity varies only slightly. If the metal of the electrode touches the skin, burns are produced by a much lower current, apparently because of excessive current density at the point of contact (Fig. 1). In this experiment, a current of 10 milliamperes was applied for 15 minutes through a thickly padded electrode to a rabbit's abdomen without causing burns. However, when a thin cross shaped metal sheet was placed between the padded electrode and the skin, the same current produced burns, but only where the metal touched the body. An otherwise safe current applied through a well padded electrode may cause a burn if contact between electrode and skin is loose. This condition is frequently painful and is probably caused by uneven distribution of the current, since the pain subsides when the electrode is pressed firmly to the skin. For a similar reason the application of an electrode over pustules or broken skin results in pain and burns since most of the current enters the body through these low resistance areas. With electrodes of equal size and current distribution, burns are produced at the cathode and at the anode with about the same strength of current and duration of application.

The formation of acid and alkali on the electrode padding has been described by several authors (Challiol and Laquerrière,³ Hirsch,¹⁰ Shaffer²⁰) and has been regarded as a contributing factor in the development of burns. Consequently, attempts were made to prevent these irritants from coming in contact with the body, for example, dipping the cathode in a weak acid in order to neutralize the hydroxide (Inchley,¹¹ Rutenbeck¹⁸).

We have studied this problem by using, instead of the customary padded electrodes, special electrodes which consisted of fluid-filled glass cylinders 10 cm. long, 2.5 cm. in diameter and with two side outlets, 2.5 cm. and 7.5 cm. from the end. One edge of the cylinder was ground, permitting, with a slight pressure and a little vaseline, a watertight seal between the cylinder and the skin. The cylinders were filled with water or saline and connected with the source of current by an immersed platinum wire. The two outlets on each cylinder permitted a continuous flow of fluid making possible the continuous removal of all electrolytically formed products.

The minimum currents necessary to produce burns within 40 minutes were determined with saline flowing through the cylinders and with saline standing in the cylinder. As a control, identical currents were applied through a pad electrode, wetted with saline and covering the same area. The current required to produce burns was the same in every instance.

Since it was expected that the replacement of saline with distilled water would reduce the formation of caustics, the above experiments were repeated under these conditions. The results however, were the same; the fluid in the anode and cathode cylinders continued to show a considerable acid or alkaline reaction. Apparently the sodium chloride present in the tissues migrates through the skin, permitting the formation of sodium hydroxide and hydrogen at the cathode and hydrochloric acid and oxygen at the anode. However, when the contents of the cylinders, after severe burns had been produced, were applied to corresponding skin areas for periods up to 3 hours, but with no current flowing, no visible irritation was produced. Similarly negative results followed the application of sodium hydroxide and hydrochloric acid solutions one hundred times as concentrated as that in the cylinders, indicating that iontophoretic burns are not caused by the contact of the acid and alkali with the surface of the skin. Rein¹⁷ has reported that by decreasing the current and increasing the time of application, irritation following an iontophoretic treatment can be eliminated. Under these conditions, while the quantity of electrolytic products formed remains the same, the rate of their formation is slower and thus the possibility of local accumulation is reduced. We have confirmed this observation; 30 milliamperes for 15 minutes produced burns, while 15 milliamperes passing through the same electrode for 30 minutes caused no visible irritation.

Hill and Taylor⁹ have recently reported that wetting the anode electrode with weak hydrochloric acid causes pain at a lower current density than wetting with saline. We have not only confirmed these findings, but also observed that the addition of the weak acid causes burns at a lower current density. In Figure 2 are shown four anode areas on a rabbit's abdomen to which the same current density was applied for equal lengths of time. Three of the pads were wetted with hydrochloric acid in concentrations of 0.001 %, 0.01 % and 1 % and the fourth with saline. It can be seen that the area wetted with the strongest acid was severely burned, while that under the 0.001 % acid appeared as normal as that under saline. If, on the other hand, a 1 % hydrochloric acid was placed on the skin without current flowing, no visible irritation was produced. Since in our previous experiments with fluid-filled electrodes the acid formation during the iontophoresis never exceeded 0.001 %, it appears that acid formation at the electrode is without influence on the development of burns. Lewis and Zotterman¹⁴ and Hill and Taylor⁹ have shown that the

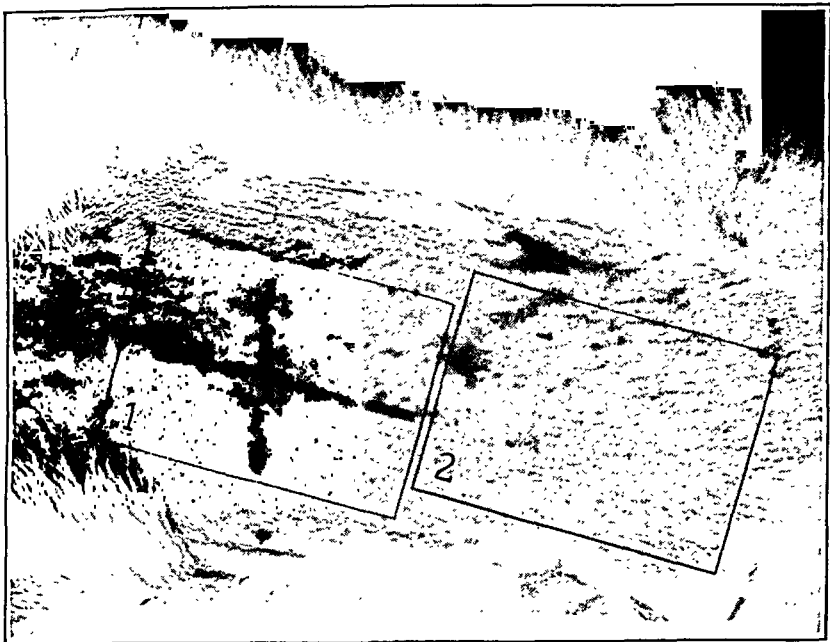


FIG. 1.—Effect of uneven distribution of current. Area 2: 10 milliamperes flowing for 15 minutes through a well-padded electrode. Area 1: the same current flowing for the same length of time, but with a thin, cross-shaped metal sheet placed between the padded electrode and the skin.

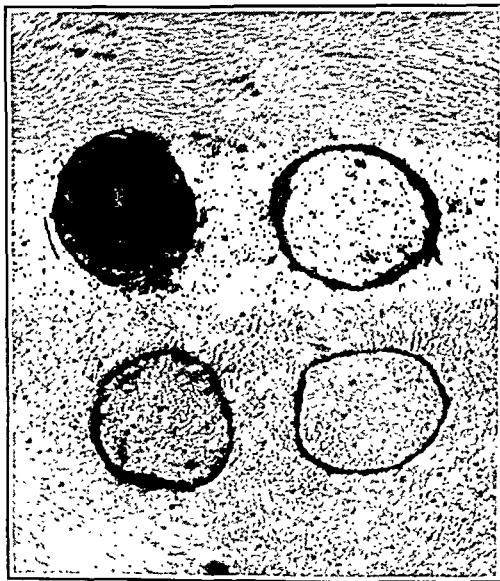


FIG. 2.—Influence of acid on formation of burns on anode area. Ten milliamperes passed for 6 minutes through areas of 6 sq. cm. using the following to wet the electrode padding. Area 1 (upper left): 1% hydrochloric acid. Area 2 (upper right): 0.01% hydrochloric acid. Area 3 (lower left): 0.001% hydrochloric acid. Area 4 (lower right): 0.9% sodium chloride.

hydrogen and oxygen liberated within the body during the passage of the galvanic current destroy the surface layer of the skin. They place greater emphasis on the physical injury caused by minute gas bubbles than on the chemical irritation.

Heat, due to sparking or to the high resistance offered by the skin to the passage of the current, can also be discounted as a cause of burns, since the possibility of sparking is eliminated in the experiments in which burns occur under the fluid-filled electrodes. Furthermore, our measurement of the skin and subcutaneous temperature with thermo-needles (Table 1) confirmed the earlier observation by Shaffer²⁰ that no increase of temperature takes place during the passage of the current which could cause burns. The slight rise of temperature observed by Turrel²¹ is due to the vasodilator effect of the galvanic current itself and therefore can not exceed the temperature of the circulating blood.

TABLE 1.—SUBCUTANEOUS SKIN TEMPERATURE DURING PASSAGE OF GALVANIC CURRENT.

Time.	Current.	Temp., ° C.	Remarks.
1:37	None	34.2	
1:42	None	34.2	
1:45	None	34.2	
1:46	16 m.a.	34.2	Burns produced in vicinity of thermo-needles
1:48	16 m.a.	34.4	
1:50	16 m.a.	34.6	
1:58	16 m.a.	34.6	

Since the formation of hydrochloric acid and sodium hydroxide in the electrode cylinders filled with distilled water indicated a migration of chlorine and sodium ions from the body, the possibility of pH changes within the skin and subcutaneous tissues was investigated. The potentiometric method of pH determination was selected as the most accurate and convenient. A specially constructed L-shaped glass electrode, the tip of which was drawn into a capillary to facilitate insertion under the skin, was used with a similarly shaped calomel electrode.* Continuous readings of the normal pH of the subcutaneous tissue in the area directly underneath the electrode were first taken for 10 minutes. Iontophoresis was then started and pH readings were taken at about 5-minute intervals during the following hour.

The pH of the tissue changed considerably during the passage of the galvanic current (Fig. 3). At the anode the tissues became increasingly acid, while a change in the opposite direction took place under the cathode. The degree and rapidity with which these changes occurred depended on the current density.

In the majority of cases the iontophoretic burns are due to faulty design or application of the electrodes. However, they may occur even under ideal conditions if the current density is excessive. It is,

* We wish to thank Dr. Nelson R. Trenner of the Merck Research Laboratories for the construction of these electrodes.

therefore, not only necessary to observe all precautions associated with the application of the electrodes, but also to limit the current density. Since it is known that an excessive current density usually results in pain, it was investigated whether a definite relation exists between the current density producing pain and that producing burns.

The following experiments on dogs and rabbits were therefore performed: Electrodes were applied to the shaved abdomen of non-anesthetized animals and a current of increasing strength passed until the animal indicated a feeling of discomfort by a sudden change in respiration. The animal was then anesthetized and the minimum current necessary to produce burns determined. The ratio between these two currents was usually approximately 3 : 4. This margin

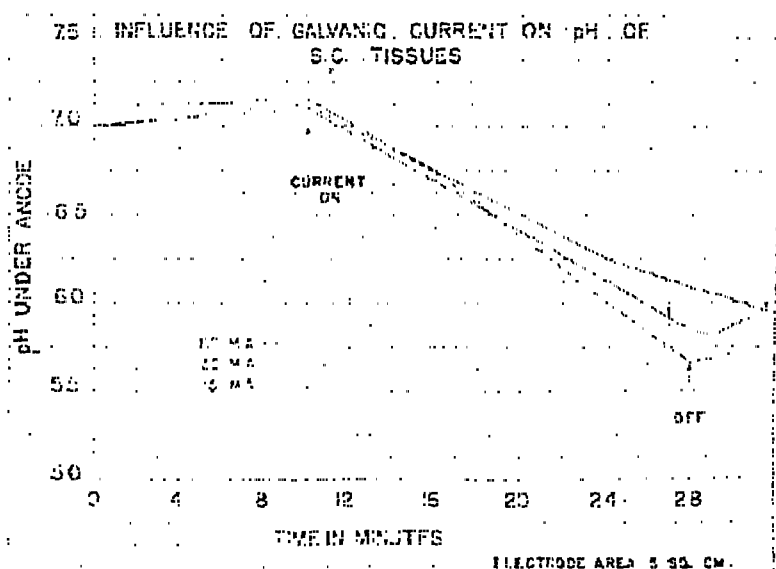


Fig. 3.—Influence of galvanic current on the pH of the subcutaneous tissues under the anode.

is so narrow that it is inadvisable to depend on pain sensation as a criterion for the prevention of burns, and another means for keeping the current within safe limits is necessary.

Data concerning safe current densities can be found in the literature (Cumberbatch,⁶ Kovacs¹³), but they differ so greatly (up to 10 times) that the discrepancy cannot be explained by experimental errors, but must rather be due to variations in technique. One of the factors in these variations is the area of the electrode. This was investigated in human subjects by passing current through a set of eight electrodes applied to the forearm, leg, and abdomen, ranging in size from 3.2 to 400 sq. cm. The current was increased at the approximate rate of 15 milliamperes per minute until pain was felt. The values obtained in 6 different subjects were strikingly similar (Fig. 4). It must be emphasized, however, that these experiments

were performed under optimal conditions, namely observing subjects and correct application of the electrode. The experiments with animals showed that a moderate increase of the current above the pain threshold is likely to result in burns. That this is also true in man is indicated by the reaction of two of our subjects who were apparently less sensitive to pain and tolerated higher current densities than the others (Fig. 4). They developed, at the site of application, a rash with formation of wheals which persisted for several days, while a visible skin reaction was completely absent in the other 4 subjects tested with somewhat lower currents. Since it is well known that various parts of the body differ greatly in their

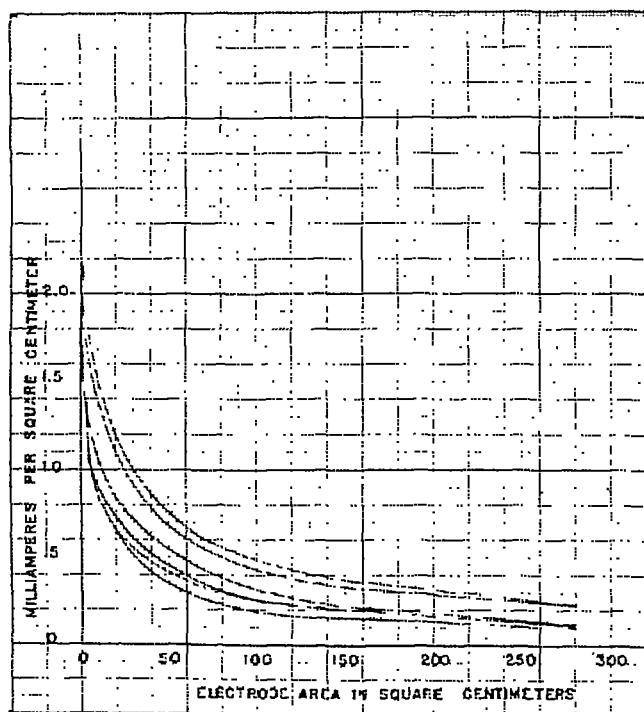


FIG. 4.—Influence of electrode area on maximum tolerable galvanic current density.

sensitivity toward faradic current, it was investigated whether a similar condition existed for galvanic current. In experiments in humans, the galvanic voltage and current necessary to produce pain were measured simultaneously. When the comparison was based on the voltage the results were similar to those observed with faradic stimulation. However, when the milliamperage was used as a basis for comparison the various regions of the body showed only slight differences in sensitivity.

In view of the fact that the curves shown in Figure 4 represent current maxima tolerable for a short time only, it seemed interesting to investigate whether current values taken from a curve of similar

shape but on a lower level could serve as a practical means for selecting a safe current limit.

We therefore constructed a curve (Fig. 5) based on the approximate current densities used in a large number of clinical applications* and having a shape similar to that of Figure 4. Its validity was tested by applying iontophoresis without therapeutic ions with electrodes of various sizes to different parts of the body of 20 subjects of both sexes varying in age from 18 to 55 years. Current values taken from the constructed curve were applied for 15 minutes. Our expectation that no discomfort or undesirable skin reaction would result was substantiated in every case.

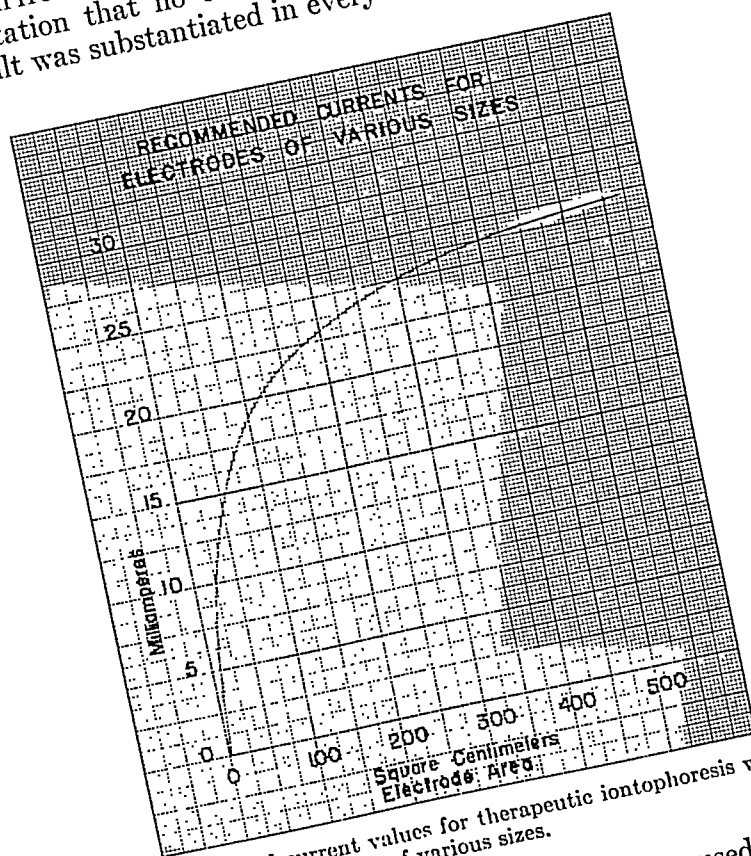


FIG. 5.—Recommended current values for therapeutic iontophoresis with electrodes of various sizes.

Summary. 1. Galvanic burns are probably caused by electrolytic changes within the tissues and not by the generation of heat or sparking between the electrode and the body.

2. These electrolytic changes result from extreme current densities due to excessive milliamperage or uneven conductivity over the electrode area (electrode metal touching body, insufficient thickness of padding, or existing skin defects).

* We are indebted to Dr. I. S. Wright for supplying this information from the records of the Post-Graduate Hospital, New York.

3. The accumulation of caustics formed in the electrode is insufficient to produce burns, as shown by the application of hydrochloric acid or sodium hydroxide one hundred times as concentrated as found in the electrode padding.

4. The pH of the subcutaneous tissues under the anode or cathode shifts during iontophoresis toward the acid and alkaline side respectively.

5. The sensitivity of various parts of the human body to galvanic stimulation is practically uniform.

6. The ratio between the galvanic currents required to produce pain and burns was found to be approximately 3 : 4.

7. The safe current density varies with the size of electrodes.

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EXPERIMENTAL STUDIES UPON THE TOXICITY OF BENZEDRINE SULPHATE IN VARIOUS ANIMALS.*

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FROM a previous study of the effects of large doses of benzedrine sulphate (amphetamine sulphate) on the albino rat,¹⁰ the conclusion was drawn that in this species the minimum lethal dose varied with the weight (age) of the animal from about 35 to 200 mg. per kilo; that the greatest non-toxic dose amounted to about 2 to 5 mg. per kilo; and that the failure of repeated sublethal doses to produce detectable

* Aided by a grant from the Smith, Kline and French Laboratories, Philadelphia.

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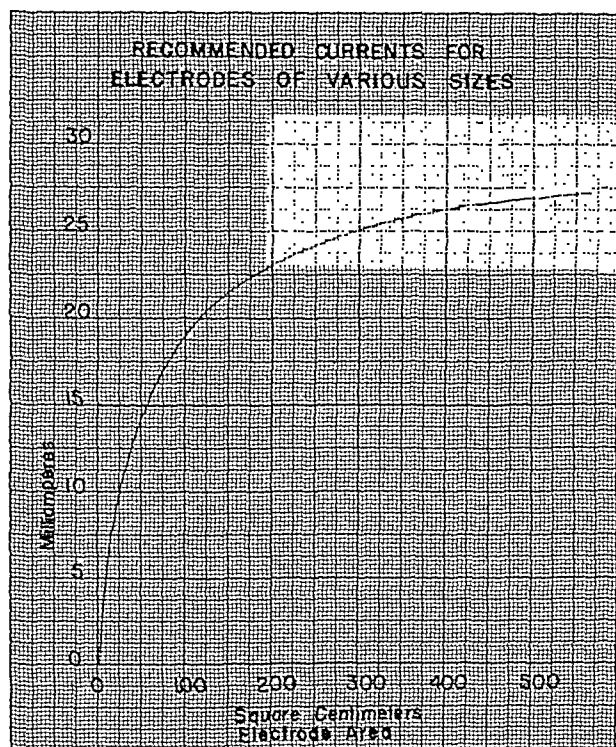


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lesions indicated that there should be a considerable margin of safety in the proper therapeutic use of the drug. We also observed tolerance changes, namely a greater susceptibility during the first 9 days of the experiments, and a marked increase in tolerance thereafter.

In man, similar experiences have been recorded by most observers. After therapeutic doses, which according to a Report of the Council on Pharmacy and Chemistry^{2c} should not exceed 60 mg. per day (1 mg. per kilo), it is true that in a number of cases tremor, sweating, dryness of mouth, loss of appetite, loss of weight, and other unpleasant symptoms made their appearance. However, there were no effects which could be considered as seriously harmful.

Similar observations have also been made with considerably larger doses. Thus, Matthews¹⁴ has given 90 mg. per day over long periods (1 to 2 mg. per kilo); Korns and Randall¹² have treated patients with orthostatic hypotension with 150 mg. daily for 6 months; Solomon, Mitchell and Prinzmetal²³ administered to 1 patient 160 mg. per day for 3 weeks (2 to 3 mg. per kilo); Davidoff and Reifenstein⁷ even gave to 1 patient 200 mg. in 1 day (3 to 4 mg. per kilo), and Robinson,¹⁸ 50 mg. every 3 hours (or 250 mg. daily). None of these observers noticed any truly harmful effects. Furthermore, Dr. E. M. MacKay has kindly furnished us with a report on a man of 67 who in 1937 accidentally took between 300 and 800 mg. (most likely 450 mg., *i. e.*, 5 to 6 mg. per kilo). When he was first seen on the second morning "the pressure was raised. He was extremely excited, appearing somewhat 'wild-eyed,' and was very apprehensive. His heart action was violent, and the palpitation bothered him a great deal. Because of his apprehension he had remained relatively quiet. He received Nembutal on the second day, but no (other) therapy. Recovery was uneventful, and he is all right at the present time." And finally, Waud²⁵ has reported observations on 8 remarkable experiments in a young man. The drug was given by means of 2 inhalers at intervals of 7 to 10 days; the amount absorbed each time was estimated at 4 to 5 mg. per kilo. The toxic signs included dilatation of the pupils for 6 to 12 hours, marked dryness of the mouth for 24 hours, marked signs of emphysema of the lungs, many extrasystoles, sinus arrhythmia, tachycardia, marked rise in blood pressure, extreme loss of appetite for 2 to 3 days, and loss of weight for a week, amounting to 10 to 14 pounds. However, there was no cyanosis, no vomiting, no nausea; the electrocardiogram was normal before and after the inhalation; and there were no bad after-effects.

Concerning the tolerance of benzedrine, it was observed by Nathanson¹⁶ that older persons seemed to tolerate more of the drug than young people. Giving repeated doses, Solomon, Mitchell and Prinzmetal²³ found no evidence of increasing tolerance. Wilbur, MacLean and Allen,²⁶ on the other hand, noticed that "the effect wore off." This was particularly striking in patients who were in

a state of depression; whereas cases of narcolepsy seemed to continue to respond well. This experience has been confirmed by the experiments of Waud:²⁵ "A definite tolerance of the body for benzedrine is slowly built up, and increasing doses are necessary to produce the original effects."

However, several warnings have also been published. An editorial writer^{2a} states that "cases of collapse, fainting and insomnia have been reported to the student health physicians. Dr. Ruth Boynton issued a warning in the *Minnesota Daily* against the use of this drug by students. . . . and according to *Time*, deans and officials of other colleges are finding it necessary to issue similar warnings." The same journal^{2b} states that the use of the drug "over long periods is certainly not without danger, particularly to the circulatory system." Anderson and Scott³ saw collapse, vomiting and heart-block with an occasional extrasystole in a patient who suffered from involutional depression with paranoid ideas after receiving 30 mg. (0.4 mg. per kilo); Davies⁸ observed collapse, vomiting and aplastic anemia in a student who before and during school examinations took first 20 mg. daily for 6 days, and thereafter 10 mg. daily for 3 days, and after an interval of 5 days, 10 mg. daily for another 4 days; and Matthews¹⁴ mentioned that a colleague had reported to him that after taking 30 mg. during a period of strain with physical exhaustion he experienced temporary tachycardia, rise in blood pressure, dilated pupils, insomnia, nausea and vomiting. Moreover, Apfelberg⁴ has recently reported a case of what appears to be acute benzedrine poisoning. The man, an elevator operator of 29 years, a psychoneurotic, probably took 140 mg. (2 mg. per kilo), and developed unconsciousness, collapse and shock. This patient, too, recovered from the intoxication. Finally, Dr. E. M. MacKay has kindly given us details of a very interesting case: "The individual was a laboratory technician, male, 27 years old, who, as we learned later, had a manic depressive history. He weighed 130 pounds. We know definitely that he weighed out 350 mg. of benzedrine sulphate, which he took along with several glasses of whiskey and soda. Two hours later when he appeared at his home he was already showing evidence of considerable cerebral irritation, and told his wife what he had done. He was excited and told of the incident as an attempt at suicide, although actually it was designed to obtain sympathy. The stomach was washed out a few minutes later, between 2 and 2½ hours after taking the drug. . . . The patient received 6 gr. of sodium amytal and was put to bed. He disappeared in the middle of the night, and was found nude on the seal rocks one hundred yards off the shore not far from the hospital, the following morning at day light. He was suffering from exposure when rescued, but he was quite coherent in conversation, although euphoric, excited and irritable. His blood pressure was raised. He was put to bed, but disappeared the following morning. At the

time of his disappearance a bottle containing between 20 and 30 grams of benzedrine sulphate was removed from the laboratory shelf and emptied. He was found two days later with the remnant of this drug in a folded paper. He gave a history of having been eating pinches of it continuously. When taken in this manner it has a slightly irritant action on the mucosa, and there was evidence of this action about the lips and gums. When found, his automobile was stuck in the sand near the surf about fifteen miles down the coast from here. The patient was drawing meaningless words in the sand, presumably as signals to aeroplanes which were circling overhead. He was in very bad shape physically. We know practically nothing of where he was or what he did during the two days that he was out of our ken. Several indications from gasoline purchases and his automobile speedometer show that he had travelled between 400 and 500 miles, going into an interior valley and coming back again. How much of the drug he took during this episode I really do not know, but feel certain that it was a great deal. He stated that he had taken it continuously, and had lost only $\frac{1}{4}$ teaspoonful. Upon hospitalization and the administration of barbiturates he made an uneventful recovery; but of course, he is still a manic depressive."

Though it is obvious that the last 2 cases were true cases of benzedrine poisoning, it should not be overlooked that all these persons when they took the drug were either physically or mentally exhausted or disordered and that the dosage was far beyond therapeutic limits. These cases can therefore not be regarded as evidence for a toxic character of the drug in reasonable amounts; though they do show that in cases of physical or mental exhaustion the drug should be administered with extra caution.

Since it seemed desirable to learn more about the toxicology of benzedrine experimentally, we have continued our studies by examining a greater variety of animals, and by extending experiments over a longer time. Special attention was paid to ascertaining the lethal dose, changes in tolerance, and the largest non-toxic dose. We also include a pathologic study of the brains by Dr. F. H. Lewy.

Material and Methods. For these experiments we used 71 guinea pigs, 50 rabbits, 9 monkeys, 24 dogs, and 2 sheep. The weights of the animals are given in Table 1.

The methods employed were essentially the same as those which we used in our previous study.¹⁰ The guinea pigs, rabbits, monkeys, and sheep received the drug subcutaneously; the dogs, by mouth. The individual doses given are found in Table 1.

The blood picture was determined from a sample of blood from the ear vein (in rabbits and dogs) or from an incision in the dorsal surface of the tail (in monkeys). For the morphological study, sections of liver, kidneys, adrenals, heart, aorta, intestine, spleen, lungs and bone marrow were stained with hematoxylin-eosin, Azur II-eosin, and Sudan III; and sections of brains were treated with various special stains for ganglion cells, nerve fibers and Schwann's sheaths.

TABLE 1.—LETHAL DOSE OF BENZEDRINE IN DIFFERENT ANIMALS.

Weight of animals (gm.).	Dose mg./1000 (gm.).	No. of animals used.	No. of animals dead after injection (expressed cumulatively).					
			1st.	2d.	Injection. 3d.	4th.	5th.	6th.
Guinea pig 95 to 200 (young)	20	4	0	2	2	2	2	2
	25	4	1	1	1	2	2	2
	30	4	1	1	1	2	3	3
	40	4	2	2	2	3	3	3
	50	4	2	2	2	3*	3	3
	60	4	0	1	1	1	1	4*
	80	3	1	2	2	2	3	
	100	4	1	3*	4			
	150	4	3	4				
	200	2	2					
350 to 720 (adult)	20	2	0	0	0	0	0	0
	25	4	0	0	0	0	0	0
	30	4	0	0	0	1†	2	2
	40	4	0	1	3	3	3	3
	50	2	1‡	1	1	2		
	60	4	0	2	3	4		
	80	4	1	4				
	100	4	2*	4				
	150	4	2	4				
	200	2	2					
Rabbit 400 to 470 (young)	25	2	0	0	0	0	0	0
	30	2	0	0	1	1	1	1
	40	2	0	2				
	50	2	2					
	100	2	2					
1320 to 2280 (preadult)	20	4	0	0	0	0	0	0
	30	4	1§	1	1	1	1	1
	40	3	0	0	0	0	0	0
	50	2	1	1	2			
	60	2	2					
	100	2	2					
2510 to 4380 (adult)	15	4	1	1	1	2	2	2
	20	4	2	3	3	3	3	3
	30	2	2°					
	40	2	2					
Monkey 2930 to 3270 (young)	2.5	1	0	0	0	0	0	0
	5	1	1					
	10	1	1					
	15	1	1					
	20	1	1					
3795 to 6440 (adult)	5	1	0					
	10	1	0					
	15	1	0	0	0	0	0	0
	25	1	1					
Dog 7000 to 26600 (adult)	10	3	0	0	0	0	0	0
	15	3	0	0	0	0	0	0
	20	2	1¶	1				
	25	1	1					
Sheep 35650 to 42320 (adult)	10	1	0	0	0	0	0	0
	15	1	1					

* One of these guinea pigs had abscesses in the liver.

† This guinea pig had acute diffuse liver necroses.

‡ One of these guinea pigs had subacute diffuse liver necroses.

§ This rabbit had a confluent bronchopneumonia.

° One of these rabbits had nephritis and marked coccidiosis.

¶ The other dog received but one injection.

Results. 1. Lethal Dose. If we consider as the minimum lethal dose one which kills half or more of the animals treated, we find (Table 1) that in young rabbits weighing 400 to 2280 gm., this dose

is 50 mg. per kilo; in adult rabbits weighing 2510 to 4380 gm., 20 mg. per kilo; in young monkeys weighing 2930 to 3270 gm., 5 mg. per kilo; in adult monkeys weighing 3795 to 6440 gm., 20 to 25 mg. per kilo; in adult dogs, 20 mg. per kilo, and in adult sheep, 15 mg. per kilo. In guinea pigs, on the other hand, the lethal dose could not be strictly defined. This was true at least for the young guinea pigs weighing 95 to 200 gm., the lethal dose of some of which was 40 to 50 mg. per kilo, while others survived with as much as 60 to 100 mg. per kilo.

Comparing the lethal doses in our different species (including the rats which we studied previously), we find (Table 2) that the lethal dose decreases with increasing weight of the species; and also with increasing age (and weight) of individuals of the same species. The only exception to the latter are the monkeys, the younger of which died with a single dose of as little as 5 mg. per kilo; while the older ones died only with 20 to 25 mg. per kilo. It is true that all the young monkeys were *Macacus rhesus*, while 3 old ones were green monkeys. But the fourth old monkey was a *Macacus rhesus* too. The latter first received 5 mg. per kilo, and thereafter, at intervals of 1 week each, increasing doses, once a week, up to 60 mg. per kilo (5, 10, 15, 20, 30, 60 mg.) without succumbing to the drug. Therefore the difference between the young and old monkeys can hardly be explained by differences in race. However, the older monkeys were well accustomed to man, while the younger ones were very much afraid. As a matter of fact, one was so excitable that it fainted occasionally when it was approached. Since we have evidence that in man the effect of benzedrine varies considerably with the mental condition of the person, it may well be that the greater susceptibility of the young monkeys was at least in part due to their greater mental lability.

2. *Tolerance.* In almost all cases, an animal received equal amounts of the drug at each dose, at least for the first 9 days. The second injection was given 3 days after the first; the third, 2 days after the second; and thereafter the animals received daily injections 6 days a week. Using this method, it was found that some guinea pigs and rabbits which survived a first sublethal dose succumbed after the same dose when it was first repeated, or perhaps later (Table 1). Of 61 guinea pigs receiving such doses, 17 died after the first, 17 after the second, 4 after the third, 7 after the fourth, 3 after the fifth, and 3 after the sixth injection; and of 21 rabbits, 5 died after the first, 3 after the second, 2 after the third, and 1 after the fourth, ninth and tenth injection respectively. However, this response was observed only in guinea pigs and rabbits (as in rats); in monkeys and dogs it was not noted.

In the present series of experiments a considerable percentage of animals died after the second injection, given 3 days after the first. In view of this delay, the explanation which we offered in the case

of our rats, namely that this effect was perhaps due to incomplete elimination of the drug during the interval, may not be the only explanation here. It is true that the higher number of casualties among the guinea pigs after the fourth injection could be explained by such an assumption, for this was the first injection given after an interval of but 24 hours; in the other cases, however, the possibility cannot be excluded that there was a true decrease in tolerance to begin with, and that this decrease disappeared within a fortnight.

If the injections were continued beyond this period, no more animals were lost, with the exception of 3 of our dogs, 2 of which received daily injections of 15 mg. per kilo, and the third 10 mg. per kilo, dying after $1\frac{1}{2}$, $4\frac{1}{2}$ and $6\frac{1}{2}$ months respectively. But these animals had steadily lost weight; they had developed a marked anemia; and at autopsy the 2 which survived for the longest time showed marked skin and eye lesions, such as loss of hair, eczema, ulceration, and partial blindness. Dr. H. L. Ratcliffe, who was good enough to examine these animals, stated that they did not suffer from alopecia. Since these dogs were the only ones that died in this way, and since they received the highest sublethal doses that dogs can stand, it cannot be denied that the benzedrine was actually concerned in their death, though it could hardly be maintained that they died from benzedrine directly. As these dogs died during August and September, and as their food had deteriorated in the summer heat, we are inclined to believe that they actually died from malnutrition, possibly from a vitamin deficiency; and that the benzedrine was merely a precipitating factor, which by lowering the appetite of the dogs decreased the intake of their low quality food to such an extent that it became inadequate.

That the higher susceptibility while taking benzedrine actually disappeared within a fortnight is best illustrated by the fact that thereafter in most animals the dose had to be increased considerably beyond the minimum lethal dose to have a lethal effect (Table 3). This was most striking in rabbits, monkeys and sheep whose lethal dose could be strictly defined; whereas in the guinea pigs, whose lethal dose varied a great deal, increased tolerance was present too, but not to the same degree. As in some of these animals the lethal dose had to be increased 10 times to have a lethal effect, this increase in tolerance is very definite.

3. *Greatest Non-Toxic Dose.* In order to find the greatest non-toxic dose we have carefully recorded our clinical observations; and in addition, we have thoroughly studied the morphology of the animals, after killing them at various intervals.

A. *Clinical Observations.* The *general behavior* of the animals when under the influence of the drug was much alike in the different species studied in this investigation, though of course there were some noticeable differences, and much like that of

our earlier rats.¹⁰ They became excited, showed abnormal motility and queer movements; and the guinea pigs, rabbits and monkeys gnawed violently at the metal cages or at their chains. Some rabbits were even found to gnaw at their own feet or thoracic skin, 1 animal damaging itself so badly that it had to be killed; and 1 of the 2 sheep was seen to chew the wool of its feet. These reactions were definitely present after 10 mg. per kilo in preadult rabbits, and after 5 mg. per kilo in monkeys.

Rabbits about to die from the drug appeared to be paralyzed in their hind legs. Most of them lay down quietly to "fade away." Some, however, cried suddenly; but thereafter were quiet again. In 2 rabbits which received 50 and 100 mg. per kilo we observed what appeared to be tremor 1 to 2 hours before the animals died. In 2 animals, which received 10 and 15 mg. per kilo, we observed convulsive movements shortly before death.

Monkeys about to die sat down as a rule, apparently because they were exhausted. Occasionally they jumped up again, but soon fell back down on their bellies. Of 5 monkeys, which were closely watched while dying, 2 which received 10 and 15 mg. per kilo "faded away." Two, which received 25 and 150 mg. per kilo, however, showed definite convulsions shortly before they died; while the fifth which received 20 mg. per kilo presented what appeared to be abortive convulsions.

The 1 sheep that received a lethal dose fell on its belly after 15 minutes and remained unable to rise. After $2\frac{1}{2}$ hours it turned on its side, was unable to return to its former position, and was found dead the next morning.

As to the *eyes*, dilatation of the pupils and absence of reaction to light was constantly present in all species. In the rabbits, both dilatation and absence of reaction was found after 10 mg. per kilo or more, while 5 mg. per kilo or less were without such an effect. The disturbance lasted the longer, the larger the dose. In the monkeys, dilatation of the pupils and absence of reaction to light were missing only in the 1 animal which received less than 5 mg. per kilo. In addition, slight conjunctival injection was casually observed in rabbits, monkeys and dogs.

Dryness of the *mouth* was suggested in some animals; marked salivation was observed in some dogs. It was very marked in 1 monkey and in 1 sheep. *Respiration* was greatly accelerated in most animals which received larger doses. In some rabbits it was up as high as 250 per minute. The action of the *heart* was studied in 2 rabbits which received 30 and 50 mg. per kilo. The electrocardiogram, for which we are indebted to Dr. F. C. Wood, showed first bradycardia and sinus arrhythmia, and after 15 minutes marked tachycardia, with a rate of 300 to 350 per minute, which persisted. There were no other changes that were surely not due to the cardiac rate.

Loss of *weight*, or in the case of growing animals retardation of

growth, was about the same in all species. In our guinea pigs both were invariably present. However, the smallest dose they received was 20 mg. per kilo. In preadult rabbits no retardation of growth was noted, with the smaller doses, except in 1 rabbit which got 5 mg. per kilo. Of 11 rabbits, which received 10 mg. per kilo or more, 3 showed a moderate and 2 a marked retardation of growth, and 6 an actual loss of weight. However, these changes were present only in the first 2 or 3 weeks; thereafter all rabbits grew again normally. Of the adult rabbits, all showed a marked loss of weight; however, all received 15 mg. per kilo or more. Of the monkeys, the 2 which were followed for some time lost weight considerably. An old green monkey which received 15 mg. per kilo for more than 5 months daily continued to lose weight all the time, amounting to about 23%. A young *Macacus rhesus* which received increasing doses from 2.5 to 165 mg. per kilo lost about 20%. Of our dogs, one which received $\frac{1}{2}$ mg. per kilo daily showed a temporary loss of weight of about 17% during the first 3 months. Two dogs which received 1 mg. per kilo lost no weight at any time. Of 2 dogs which received 2 mg. per kilo, 1 showed a loss of 14% during the first 2 months. Of the dogs which got 5 mg. per kilo or more, finally, all showed a marked loss of weight. As we wanted to study these animals over a long time, the dose of benzedrine was adjusted to the changing weight (Figs. 1 and 2). Thus, of 2 dogs which received 5 mg. per kilo, one returned to its original weight, whereas the other remained on a lower, though even level. Of those which receive 10 mg. per kilo, 1 remained on a lower, though even level, while the other lost weight continuously. The dogs which received 15 mg. per kilo lost weight continuously. It should be noted that those dogs whose weight could be stabilized remained alive; whereas those which lost weight continuously, died eventually from malnutrition (Cf. p. 791).

B. The Blood Picture. This was carefully studied in rabbits, monkeys and especially in dogs. Of the rabbits, 20 received various doses of benzedrine, and 7 served as controls. However, since of the experimental animals 12 died from benzedrine or from intercurrent infections, and of the controls, 3 were found at autopsy to have spontaneous disease, there remained but 8 experimental animals and 4 controls for evaluation. These were followed for 5 to 6 weeks. Of the 8 test animals, all developed a moderate anemia, their erythrocytes coming down to 4.0 to 4.6 millions per c.mm., irrespective of the dose of benzedrine (2 to 30 mg. per kilo), and of the initial count, which varied from 4.8 to 6.8 millions. The anemia was macrocytic in all cases. It reached its lowest level in 15 to 22 days after starting injections; however, since 2 of our 4 controls behaved the same way, no weight can be attached to this observation. The granulocytes ("amphophiles") in the rabbit are said to range normally between 1600 and 5700 per c.mm. (Scarborough²⁰). All our normal counts were between 1700 to 5700. Considering figures above 6000 as

indicative of granulocytosis, this was present on several occasions in all 5 animals which received 10 or 20 mg. per kilo. However, there was no granulocytosis in the 1 rabbit which received 30 mg. per kilo; while 1 rabbit receiving 2 mg. per kilo and 2 controls each showed an elevated count on one occasion, and that not above 8000. In the rabbits which received 10 or 20 mg. per kilo, it rose as high as 12,100. As to the lymphocytes, all initial figures were between 2500 and 8900 per c.mm. (Scarborough's normals 1700 to 5200). Figures of 9100 to 16,100 were encountered in 4 rabbits which received 5 to 20 mg. per kilo, as well as in 3 controls.

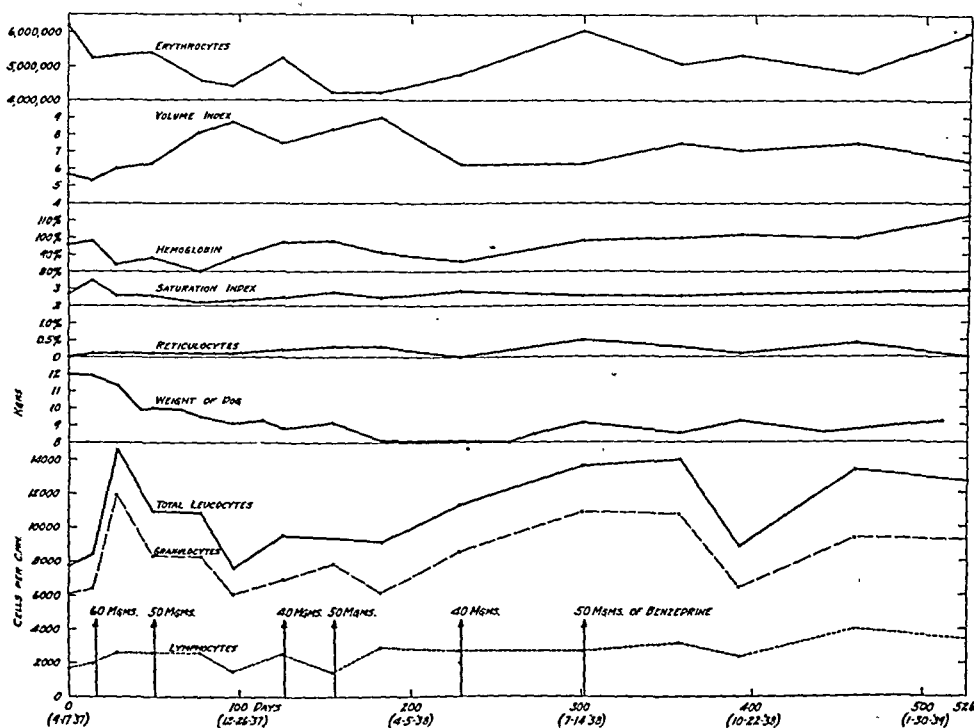


FIG. 1.—BLOOD PICTURE AND WEIGHT OF DOG 56.

Dog 56 received 5 mg. of benzedrine per kilo daily for 17 months. The arrows indicate the time when the dose was adjusted to the changing weight of the dog.

However, as these figures were obtained but once or twice on each animal, they cannot be regarded as due to the benzedrine.

Of the monkeys, the blood picture was studied in all but 3; but only 2 were followed for a longer time. Monkey 1, an old green monkey which received 15 mg. per kilo daily, was studied over 4 months; and Monkey 7, a young *Macacus rhesus*, which received daily doses of from 2.5 to 165 mg. per kilo, was followed for 3 months. Monkey 1 lost weight steadily, became moderately anemic at least for 1 to 3 months, and developed a marked granulocytosis for about 2 months. Monkey 7, also, stopped growing and lost weight; it

developed a severe anemia and a marked granulocytosis when the dose was increased above 5 mg. per kilo (Table 4).

Of the 15 test dogs and 4 controls, the blood was studied in all but 5. However, 1 died after a single large dose; 6 died from pneumonia or distemper; and 3 that received 10 and 15 mg. per kilo died after $1\frac{1}{2}$ to $6\frac{1}{2}$ months, apparently from malnutrition (*Cf.* p. 791). There thus remained but 7 experimental animals and 2 controls for protracted study; these were followed for 9 to 26 months.

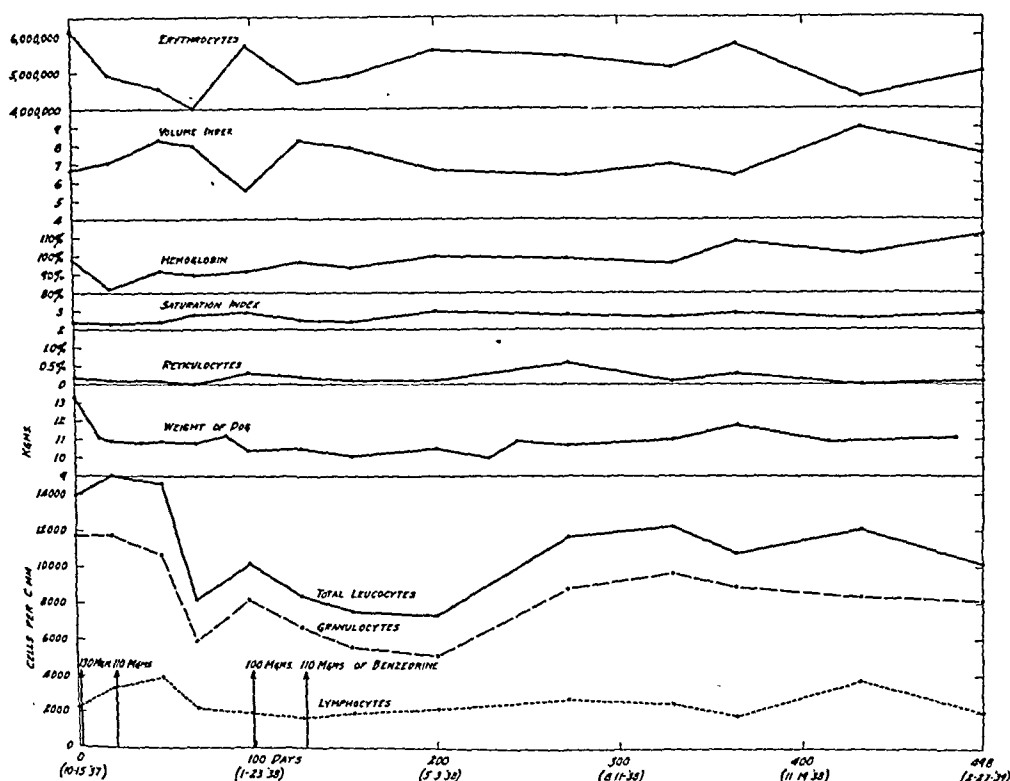


FIG. 2.—BLOOD PICTURE AND WEIGHT OF DOG 57.

Dog 57 received 10 mg. of benzedrine per kilo daily for $16\frac{1}{2}$ months. The arrows indicate the time when the dose was adjusted to the changing weight of the dog.

As to the erythrocytes, if we consider figures from 4.5 to 6.0 millions per c.mm. as normal under the existing conditions, none of our controls and none of our test animals which received 1 mg. per kilo or less developed anemia as a result of the drug. In a dog receiving 2 mg. per kilo (Dog 566), the erythrocyte count went down to 3.76 millions during the first 3 months; returned to normal for 5 months; and again went down to 3.97 millions for another 5 months; thereafter remaining normal for the last 10 months. All the dogs receiving 5 mg. per kilo or more showed a definite anemia (Figs. 1 and 2). In the 2 dogs receiving 5 mg. per kilo (Dogs 730 and 56), the anemia lasted for 5 to 6 months (lowest counts 3.67 and 4.23 millions per c.mm.). In the dog receiving 10 mg. per kilo (Dog 57),

TABLE 2.—LETHAL DOSE OF BENZEDRINE IN DIFFERENT ANIMALS.

Animal.	Weight (gm.).	Lethal dose in mg./1000 gm.
Rat	50-95	200
	100-195	50-60
	210-385	30-40
Guinea pig	95-200	40-150
	350-720	50-100
Rabbit	400-470	50
	1320-2280	50
	2510-4380	20
Monkey	2930-3270	5
	3795-6440	20-25
Dog	7000-26600	20
Sheep	35650-42320	15

TABLE 3.—INCREASE IN TOLERANCE AFTER 10 DAYS OF THE EXPERIMENT.*

		Dose in mg./1000 gm. required to kill animal. The figures indicate percentage of animals killed.						
Animal.	Injections.	5-10	15-25	30-40	50-60	80-100	150-200	300-500
Rat . . .	After 1	..	0	22	40	53	57	100
	After 6	..	0	4	4	26	37	100
Guinea pig .	After 1	..	7	19	21	33	75	
	After 6	..	0	12.5	41	50	69	100
Rabbit . .	After 1	..	21	33	83	100		
	After 6	..	11	22	33	56	89	100
Monkey . .	After 1	40	75					
	After 6	0	0	0	50	50	100	
Sheep . . .	After 1	0	100					
	After 6	0	0	0	0	0	100	

* The figures of this table have been calculated from all animals regardless of age.

TABLE 4.—CHANGES IN THE BLOOD PICTURE AFTER ADMINISTRATION OF BENZEDRINE (MONKEYS).

Date.	Weight (kilo).	Erythrocytes (mill. per c.mm.)	Hemoglobin %	Hemoglobin index.	Leukocytes (thous. per c.mm.)	Granulocytes (thous. per c.mm.)	Lymphocytes (thous. per c.mm.)
<i>Monkey 1.</i>							
1938							
1/28	5.0	4.83	87	18.0	8.9		
		4.88	88	18.0	9.1	7.2	1.9
2/1	Injection started, 15 mg. per kilo daily.						
2/5	..	4.22	87	20.6	14.0	11.0	2.9
2/19	..	4.14	78	18.8	14.4	13.0	1.4
3/5	4.35	4.21	78	18.5	17.3	13.6	3.6
4/1	4.1	4.55	79	17.4	12.7		
5/10	3.9	4.22	80	19.0	10.8		
6/2	3.8	4.95	80	16.2	9.9	7.7	2.3
<i>Monkey 7.</i>							
1938							
3/29	3.3	4.34	75	17.3	16.8	8.4	8.4
4/1	..	4.94	84	17.0	15.7		
5/10	3.8	4.51	90	20.0	12.5		
5/10	Injection started, 2.5 mg. per kilo daily until 5/30; 5 mg. on 5/31						
6/2	3.65	4.77	82	17.2	18.8	12.2	6.6
6/2	Injection continued with increasing doses from 10 mg. to 50 mg. each 2d or 3d day until 6/23.						
6/24	3.4	3.06	74	24.2	21.3	16.2	5.1

it lasted for 2 to 3 months (lowest count 4.02 millions). It should be noted (Table 5) that in general the degree of the anemia was the more severe the greater the dose of benzedrine and the heavier the loss of weight. The duration of the anemia, however, was without respect to either dose or loss of weight. There was a definite tendency to macrocythemia, while the saturation of the cells with hemoglobin and the number of reticulocytes remained rather constant (Fig. 1 and 2). While we do not hesitate to attribute the anemia of the last 3 dogs to the action of benzedrine, this is doubtful in the case of the animal which received 2 mg. per kilo; as there seemed to be a periodical variation, the counts being normal during the summer and low during the winter. As similar observations were made in at least 2 other animals which received $\frac{1}{2}$ and 1 mg. per kilo; and as it was not possible to maintain the animals under the best hygienic conditions throughout, seasonal influences cannot be excluded. Romeis,¹⁹ for instance, found increased blood destruction in the spleen of mice which accidentally were exposed to a heat of 86 to 93° F. for 2 months.

TABLE 5.—DURATION AND DEGREE OF ANEMIA AND GRANULOCYTOSIS AFTER BENZEDRINE AS COMPARED WITH WEIGHT LOSS (DOGS).

Dog No.	Dose in mg./1000 gm.	Duration of anemia (mos.).	Lowest erythrocyte count (millions).	Duration of granulocytosis (mos.).	Highest granulocyte count (thousands).	Duration of weight loss.	Maximum weight loss (%)
730	5	5-6	3.67	$\frac{1}{2}$ -1	15.6	1-2	20
56	5	6	4.23	$\frac{1}{2}$ -1	12.8	6	33
57	10	2-3	4.02	1-2	11.7	7-8	25
268*	10	Continued	2.57	3	23.6	Continued	41
729*	15	Continued	2.12	2-3	17.4	Continued	29

* These dogs died spontaneously, apparently from malnutrition.

Two of the 3 dogs that died of malnutrition had long continued blood studies. Dog 268 showed a progressive anemia together with a progressive loss of weight until death after 6 $\frac{1}{2}$ months; Dog 729 showed a marked anemia and a low weight constantly until it died after 4 $\frac{1}{2}$ months (Table 5). In the former, the erythrocyte count dropped to 2.57, and in the latter to 2.12 millions per c.mm. The size of the erythrocytes was markedly increased in the former, and moderately in the latter. The hemoglobin saturation of the erythrocytes, however, remained rather constant; the number of reticulocytes was always low, except once in 24 counts, *i. e.*, negligible as far as benzedrine is concerned.

As to the leukocytes in the dogs, there was no lymphocytosis at any time, and no granulocytosis in any animals which received 1 mg. per kilo or less, or in our controls (except for 1 dog that showed a temporary granulocytosis apparently due to infection). All dogs receiving 2 mg. per kilo or more developed a definite granulocytosis. In general, the degree and especially the duration of the granulocytosis was higher, the larger the dose of benzedrine (Table 5). In the dog receiving 2 mg. per kilo, it lasted but 1 to 2 weeks, the highest count being 16,786 per c.mm.; while in the 2 dogs which got

5 mg. per kilo it lasted $\frac{1}{2}$ to 1 month, the highest counts being 12,806 and 15,607 per c.mm.; while in the dog which received 10 mg. per kilo it lasted 1 to 2 months, the highest count being 11,739 per c.mm. In the 2 dogs that died from what we believe was chiefly malnutrition, the granulocytosis lasted for 2 to 3 months, the highest counts being 17,355 and 23,571 per c.mm.

C. Postmortem Observations. The *thoracic* and *abdominal organs* were essentially normal in all animals which survived the administration of benzedrine. This was the case even in those dogs that received 5 or 10 mg. per kilo for 2 years and longer, except that in

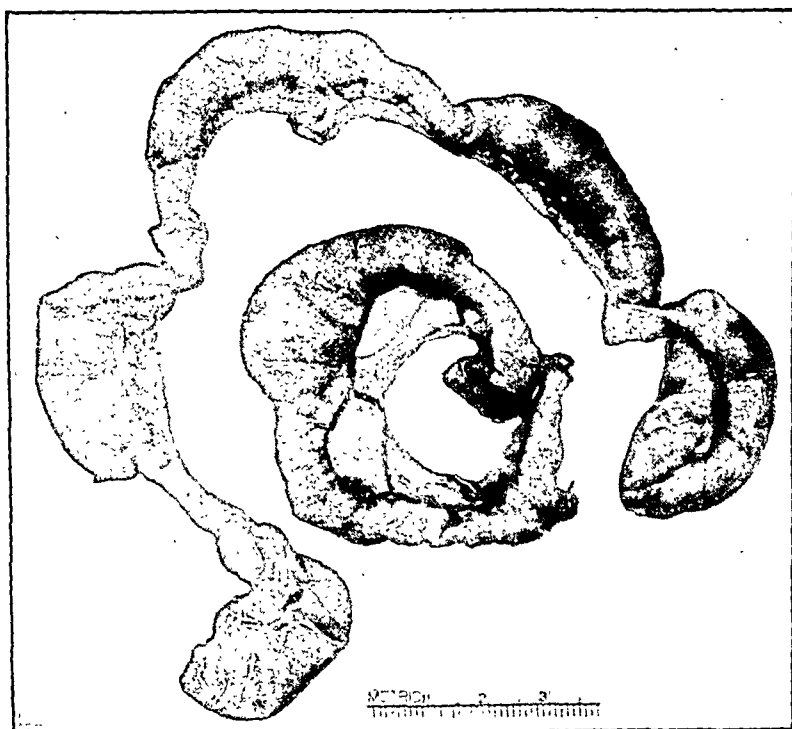


FIG. 3.—Sections of small intestine from Rabbits 57 and 60 showing antemortem constriction of lumen after the administration of lethal doses of benzedrine.

the latter the arterioles of spleen and kidneys appeared to be thicker than normal. However, there was no fatty change of the vessels, *i. e.*, no arteriosclerosis; and there were no necroses, scars, or calcification in any of the organs. As in rats,¹⁰ the livers contained but little stainable fat.

In animals dying from benzedrine, there was marked dilatation of the heart; congestion of liver and kidneys; either congestion or contraction of the spleen; air in stomach and intestine; and in some animals, subpleural and pericardial hemorrhages, as well as marked and sharply delimited constrictions of the small intestine (see Fig. 3). Contraction of the spleen was observed in 22 of 31 guinea

pigs, in 11 of 25 rabbits, in 4 of 7 monkeys, and in 1 of 2 dogs. Subpleural and pericardial hemorrhages were observed especially in rabbits and monkeys; particularly after large doses (in rabbits after 50 mg. per kilo and more, and in monkeys after 10 mg. per kilo and more). Constrictions of the small intestine (Fig. 3) were noted especially in rabbits, monkeys and dogs; and again especially after large doses (in rabbits after 30 mg.; in monkeys after 10 mg.; and in dogs after 25 mg. per kilo and more).

The only histologic lesions in the thoracic or abdominal organs of the animals which died from benzedrine that could be connected with the action of the drug were necroses in liver and spleen. Definite liver necrosis, however, were seen only in 3 guinea pigs, 1 rabbit and 1 dog; and definite spleen necroses in 7 rabbits and 1 monkey. Most of these animals had received large doses of benzedrine.

The *central nervous system* was thoroughly investigated in 3 monkeys and 7 dogs. Of the 3 *monkeys*, Nos. 2 and 5 died 1 and 5 hours, respectively, after the first injection (25 and 10 mg. per kilo, respectively); No. 7, which first received 2.5 mg. per kilo for 3 weeks, died only 1½ hours after a dose which had been gradually increased up to 165 mg. per kilo. Monkeys 2 and 7 showed convulsions; Monkey 5 did not. As to the histology of the central nervous system, Monkey 5 showed practically no changes. Monkeys 7 and 2, however, presented characteristic signs of an acute intoxication of the brain, namely venous stases, perivenous hemorrhages in the meninges, white matter of the hemispheres, and cerebellum; and toxic degeneration of the nervous cells in these regions.

Of the 7 dogs, but 1 (Dog 500) died after the first administration of a lethal dose, and that between 4 and 20 hours following the administration of 25 mg. per kilo. The brain of this dog closely resembled those of Monkeys 7 and 2 in that it showed congestion, numerous perivenous hemorrhages, and toxic degeneration of the cortical nerve cells.

Of the other dogs, a group of 4 receiving 1 to 10 mg. per kilo for 17 to 25 months without succumbing to the drug appeared to be in good health when they were finally sacrificed. Of these, Dog 57 received 10 mg. per kilo for 17 months; Dog 730, 5 mg. per kilo for 22 months; Dog 566, 2 mg. per kilo for 23 months; and Dog 267, 1 mg. per kilo for 25 months. Dog 267 showed no lesion whatsoever in its central nervous system. The other 3 presented some chronic changes, namely a slight focal thickening of the meninges, in some places with obliteration of the subarachnoid space; a moderate fibrosis with hyaline degeneration and round-cell infiltration of the arterioles and capillaries of the meninges, cortex and corpus striatum; small foci of blanching of nerve cells in the cortex (which in Dog 57 was associated with a fairly pronounced glia reaction, while in Dog 730 this reaction was questionable, and in Dog 566 it was absent), and subependymal glia proliferation in the walls

of the lateral third and fourth ventricles (which at least in Dog 566 reached the degree of true granular ependymitis). With the exception of the latter, all changes were more marked in the dog which received daily doses of 10 mg. per kilo than in the dog which got 2 mg. per kilo. The severity of these changes should not be overrated. In terms of human pathology they are comparable only to those of elderly people suffering from a mild hypertension.

The last 2 dogs studied belonged to the group of 3 which apparently died from malnutrition (Dogs 729 and 268). In both these dogs, dying $4\frac{1}{2}$ and $6\frac{1}{2}$ months after the onset of the experiment, obviously acute changes predominated; *i. e.*, congestion and toxic degeneration of nerve cells in the cortex.

Comment. Attempts to compare our results with those in the literature reveal a scarcity of comparable data. As a matter of fact, we found no reports which dealt with the tolerance or the greatest non-toxic dose of benzedrine in animals; and but three papers which contained data on the lethal dose. Hartung and Munch¹¹ found the lethal dose of benzedrine hydrochloride to be 25 mg. per kilo in rabbits if the drug was given intravenously; Alles¹ found it to amount to about 50 mg. per kilo in guinea pigs if given subcutaneously, and Searle and Brown,²² to about 30 mg. per kilo in rats when given subcutaneously and intraperitoneally. However, Hartung and Munch did not include figures on the weight (age) of their animals nor on the number of animals which they used; and Alles used but 10 animals, without giving their weight. The only study of toxicity after oral administration that we are aware of is that of Lumière and Meyer,¹³ which shows that it is much less than by subcutaneous injection.

Our experiments in general produced strikingly similar results in different animals and species. It is true that smaller (younger) animals and smaller species required as a rule larger doses per kilo to produce the same degree of reaction as in the larger animals and larger species; but qualitatively there was hardly any difference. Calculated in terms of the total dose per animal, it was found, as might be expected, that as a rule the larger individuals and species required larger total doses. The only exception to the similarity in response of the different species was the behavior of the erythrocytes, which in our rats increased in number after certain dosages; while in our rabbits, monkeys and dogs they tended to decrease. We cannot give a definite explanation for this difference. Though it is possible that the rat findings might have been the result of the technique required (repeated amputation of the tail), we hesitate to accept such an assumption as our findings were so uniform. Moreover, in man similar discrepancies have become apparent. Myerson, Loman and Dameshek¹⁵ have observed a marked erythrocytosis after giving 40 mg. of benzedrine. On the other hand, Davidoff and Reifenstein,⁷ who gave 10 to 30 mg. of benzedrine, and Bradley⁶

and Donley,⁹ who gave similar doses, were unable to detect a definite erythrocytosis; while Schube, Raskin and Campbell,²¹ who gave humans daily doses of 10 mg. orally, found first a decrease, and later an increase in the hemoglobin, but no alteration in the number of erythrocytes. The discrepancies in man, to be sure, might partly be due to differences in the doses which were given, and in the periods which elapsed between application of the drug and the time the blood was taken. In our rats, however, this explanation does not apply, for as in our rabbits, monkeys and dogs all counts were taken 24 hours after the last application of the drug. If in the rats this was really an erythrocytosis due to benzedrine, we would have to assume that this was a species difference and perhaps a redistribution rather than an increase in the total number of erythrocytes. It might be that the effect of the drug upon the blood reservoirs, such as the spleen, the mechanism which is held responsible for the increase of erythrocytes in the circulating blood after the application of benzedrine, lasted much longer in rats than in our larger laboratory animals. On the other hand, the anemia, when significant, may be taken as a true decrease in the total number of erythrocytes, due presumably to such factors as a toxic effect on the bone marrow and malnutrition.

Comparing toxicity, our results are not incompatible with those found in man. As much as 5 to 6 mg. per kilo have been taken by man without causing death; while in our various animals, from 15 to 200 mg. per kilo (with the exception of 2 monkeys) were required to cause death (Cp. Table 2).

Concerning *tolerance*, "accustoming" has been observed by Wilbur, MacLean and Allen²⁶ and Waud.²⁵ On the other hand, a greater susceptibility, as was observed during the first 2 weeks of our experiments, has apparently not been detected in man. However, it should be noted that greater susceptibility was observed by us only with sublethal doses, which in man have been given, if at all, only by Waud, who administered the drug only at intervals of a week.

If we turn now to the *greatest non-toxic dose*, reports in the literature indicate that unpleasant effects such as tremor, sweating, dryness of mouth or loss of weight have been observed with therapeutic doses (up to 1 mg. per kilo). But harmful effects did not become apparent even with considerably larger doses (up to 5 to 6 mg. per kilo), with the exception of perhaps 4 reported persons who took from 0.4 mg. per kilo to an undetermined amount of benzedrine. The latter, however, were all physically or mentally exhausted when they took the drug and therefore do not furnish unequivocal evidence as to the toxic character of the drug (see p. 788).

It is obvious that the transient variations which have been observed, such as excitement, dilatation and paralysis of the pupils, loss of weight, and even temporary anemia and granulocytosis, cannot be regarded as harmful in the terms of this study. The only

observed change which could be accepted as harmful is the chronic alteration of the small blood vessels, which in dogs was definitely present after 5 mg. per kilo; less conspicuously after 2 mg.; and not at all after 1 mg. However, this change developed only if the experiments were continued over a long time; and from the nature of the lesion it appears to have been caused by a continuously repeated elevation in blood pressure.

We may conclude, then, from the experiments as we have conducted them that, with the exception of cases of idiosyncrasy, small doses of benzedrine which do not raise the blood pressure are harmless even if given for a long time, and that even larger doses are harmless if not continued for too long a time, and if not given to patients which suffer from exhaustion or cardiovascular disease with hypertension. This view is strengthened by reports which indicate that with repeated doses the blood pressure effect gradually diminishes in man (Storz;²⁴ Reifenstein and Davidoff;¹⁷ Bahnsen, Jacobsen and Thesleff⁵). "Small" doses amount in rabbits to 5 to 10 mg. per kilo; in monkeys, below 2 to 5 mg. per kilo; and in dogs, to 1 to 2 mg. per kilo, while "larger doses" extend all the way up to sublethal doses, *i. e.*, to 2 to 5 mg. per kilo in young monkeys, and 150 to 200 mg. per kilo in young rats. The corresponding human doses remain to be detected. This is probably best accomplished by direct observation of the blood pressure; though our experimental observations seem to indicate that control of body weight and blood picture may also be revealing.

Summary. The functional and structural changes caused by continued application of various doses of benzedrine sulphate were studied, and the lethal dose, the tolerance, and the greatest non-toxic dose were determined, in various species, and at different ages. The animals used included 71 guinea pigs, 50 rabbits, 9 monkeys, 24 dogs, and 2 sheep.

The functional changes were essentially the same as previously observed in rats,¹⁰ with the exception of the behavior of the erythrocytes which did not increase in number. Instead, there developed a macrocytic anemia, the extent and the duration of which varied with the dose given.

The structural changes, too, resembled those in rats. In addition, however, we observed venous stases, perivenous hemorrhages and toxic degeneration of nerve cells in the brain in animals which died from lethal doses; and, in dogs receiving 2 mg. per kilo or more for a long time, chronic vascular lesions in brain, spleen and kidneys resembling those in mild hypertension.

The minimum lethal dose per kilo was found to be as follows: in young guinea pigs, 40 to 150 mg.; in adult guinea pigs, 50 to 100 mg.; in young and preadult rabbits, 50 mg.; in adult rabbits, 20 mg.; in young monkeys, 5 mg.; in adult monkeys, 20 to 25 mg.; in adult dogs, 20 mg.; and in adult sheep, 15 mg. per kilo.

As to tolerance, we found an increase in susceptibility during the

first 2 weeks of the experiments in guinea pigs and rabbits (as in rats). Thereafter, the animals became accustomed to the drug. This was most striking in rabbits, monkeys and sheep, and less so in guinea pigs; in dogs, it was not determined.

The greatest non-toxic dose (*i. e.*, a dose which does not induce important undesirable variations in function, or if continued over a long time, does not produce detectable lesions) was found to amount to 5 to 10 mg. per kilo in rabbits; to 2 to 5 mg. per kilo in monkeys; and to 1 to 2 mg. per kilo in dogs.

Conclusions. In our most susceptible animals, the minimum lethal dose of benzedrine sulphate was found to be about 5 mg. per kilo. From the scanty evidence available, the minimum lethal dose in man is probably not below this level, though it may well vary considerably, as in our monkeys, with the nervous constitution of the individual. In more resistant species the minimum lethal dose rises to 100 to 150 mg. per kilo.

Continued administration of benzedrine leads first to a greater susceptibility and thereafter to increased tolerance. The initial increase in susceptibility, however, is of practical importance only if large doses are applied.

Study of the maximum non-toxic dose showed that the lowest obtained was 1 to 2 mg. per kilo. Though the maximum non-toxic human dose still remains to be detected, it appears to be safe to conclude that small doses of benzedrine which do not raise the blood pressure, or which do not produce loss in weight, anemia, or granulocytosis, should be harmless even if given for a long time; and that larger doses should also be harmless, if not continued for too long a time, or given to patients suffering from severe exhaustion or cardiovascular disease with hypertension.

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ANEMIA INDUCED IN RATS BY MEANS OF SULPHANILAMIDE.

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THE purpose of this paper is to present the details of a type of anemia⁸ which has been observed in rats subsequent to the administration of sulphanilamide (para-aminobenzene sulphonamide). Toxic symptoms observed and significant gross pathologic findings will be described.

In October, 1937, Hageman⁴ reported the finding of splenic hemosiderosis in mice to which sulphanilamide had been administered. Although he made no blood counts, he attributed the deposits of hemosiderin to destruction of erythrocytes in the peripheral blood.

In October, 1937, Finklestone-Sayliss, Paine and Patrick² found little or no change in the erythrocyte or reticulocyte levels of rabbits to which a daily dose of 1.2 gm. of sulphanilamide was administered over a period of 6 weeks. However, crises, during which the leukocyte count increased, were observed, the increase being due to neutrophils; these crises were associated with the appearance of abnormal and nucleated erythrocytes in the peripheral blood.

In April, 1938, Wien¹⁴ reported the finding of lower erythrocyte and hemoglobin levels in 3 rats receiving 1.5 gm. of sulphanilamide per kg. of body weight than in control animals. He found no similar depression in 2 rats which received 0.5 gm. per kg. of body weight. No evidence of anemia was found in 2 cats and 1 dog which received 1 gm. of sulphanilamide daily over a period of 7 days.

In April, 1938, Rimington and Hemmings¹⁰ reported the finding of an increased excretion of urinary and fecal porphyrin in rats receiving daily doses of sulphanilamide. The doses were 0.4, 1.39 and 1.5 gm. per kg. of body weight and were administered over a period of a month. At necropsy, deposits of iron containing granules were found in the liver and spleen.

In May, 1938, Davis, Harris and Schmeisser¹ reported the finding of a definite reduction in the number of erythrocytes and in the amount of hemoglobin together with a slight leukocytosis in rats which received daily subcutaneous doses of sulphanilamide. The doses used were 0.5, 1, 1.5 and 2 gm. per kg. of body weight and the administration was continued over prolonged periods.

Method. In the experiments to be reported here sulphanilamide was administered daily by means of stomach tube to adult male white albino rats of the Wistar strain; average weight of the animals was 300 gm. The

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doses used were 0.25 gm. (6 rats), 0.5 gm. (6 rats), 1 gm. (18 rats) and 2 gm. (24 rats) per kg. of body weight. The drug was administered in the form of a powdered suspension in tap water in single doses, each dose being contained in 6 cc. of the suspension. The duration of administration varied from 10 days to 2 months in the various experiments.

Charts of daily food and water intake and weight were kept on the animals in groups of threes. Urinary output was measured on animals isolated in individual metabolism cages. No attempts were made to expose animals to sunlight or to protect them from it.

Data will be presented on erythrocyte, reticulocyte, leukocyte, platelet and hemoglobin levels, differential leukocyte counts, volume of packed erythrocytes, mean corpuscular volume, and linear dimensions of the erythrocytes.

Blood was obtained by ear puncture; standard methods were used for determining total erythrocyte, reticulocyte and leukocyte counts. Powdered heparin was used as an anticoagulant for the samples of blood drawn into hematocrit tubes. Hemoglobin was estimated in percentage by the Newcomer⁹ method ($100\% = 16.92$ gm.). The linear dimensions of the erythrocytes were determined by photographing the cells of the stained smear on sensitized paper and measuring the diameter of non-distorted cells by means of a micron scale. The average diameter was computed from the measurement of 100 cells in each smear. Platelets were counted in a counting chamber using 0.3% sodium citrate as the diluent.

Results. *Details of the Blood Picture.* The details of the blood picture will best be presented as observed in a group of 6 animals which received 1 gm. of sulphanilamide daily over a period of 22 days.

During the first 10 days, there occurred a progressive decrease in the total erythrocyte count and hemoglobin percentage as well as in the percentage of packed erythrocytes, while the mean corpuscular volume, red cell diameter and percentage of circulating reticulocytes increased (Fig. 1). During the remaining 21 days, although the same general trend persisted, its degree was lessened. This lessening of the degree of anemia appeared concomitantly with about 100% increase in daily water intake (Fig. 2). The apparently lessened toxic effect on the erythrocyte level might be explained on the basis of an increased elimination of the drug due to an increased fluid intake and urinary output. During this period the animals manifested evidence of marked thirst.

The color index increased from 0.78 during the control period to 0.92 at the end of the experiment. After a slight drop on the third day, the total leukocyte count increased, reaching its highest level on the tenth day, then gradually decreased toward control levels. The curve of the total number of lymphocytes followed the curve of the total leukocyte count fairly closely except from the third to the tenth days. At this time the total numbers of neutrophils and immature forms were increased (Fig. 3). During the time at which the total leukocyte count was greatest the percentage of

lymphocytes was lowest and the percentages of neutrophils and immature forms were greatest. Platelets were counted in 6 animals receiving the same dose over a period of 6 weeks, and no significant change was observed (Table 1).

TABLE 1.—RELATION OF DOSAGE TO THE DEGREE OF ERYTHROCYTE DEPRESSION.

Period of administration in weeks.	Erythrocytes in millions per c.mm.			Platelets per c.mm.
	0.25 gm. per kg.	0.50 gm. per kg.	1 gm. per kg.	
Control	10.25	10.05	9.82	823,120
1	10.15	9.38	8.70	750,000
2	9.99	8.70	7.35	830,000
4	9.66	8.65	6.48	730,000
6	9.85	8.35	6.04	795,000

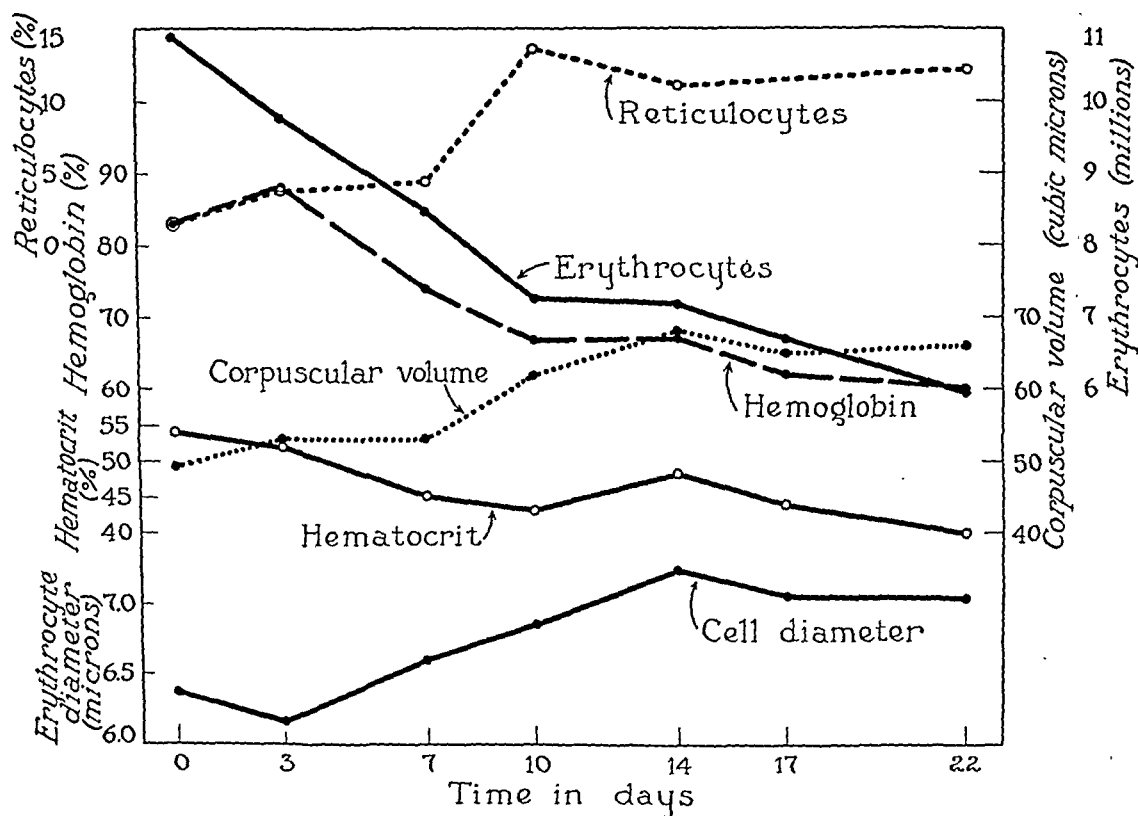


FIG. 1.—Trend in the erythroid components of the peripheral blood in a group of 6 rats which received 1 gm. of sulphanimide per kg. of body weight daily for 3 weeks (average dose = 0.33 gm.).

Effect of Varying Size of Dose Administered. In order to determine any possible relationship between size of dose and degree of depression of the erythrocyte count, the drug was administered daily in 4 different dosages to four different groups of animals com-

posed of 6 animals each. These dosages were 0.25 gm., 0.5 gm., 1 gm., and 2 gm. per kg. of body weight respectively. At the end of 10 days the percentage drop from control erythrocyte levels in the four groups was 2.9%, 10.2%, 36.1% and 42.2%, according to increasing dosage (Fig. 4). Administration of the 3 smaller dosages daily over a period of 6 weeks revealed the same trend in level of the erythrocytes, the smallest dosage (0.25 gm. per kg.) having the least, if at all, significant depressant effect. At the end of 6 weeks

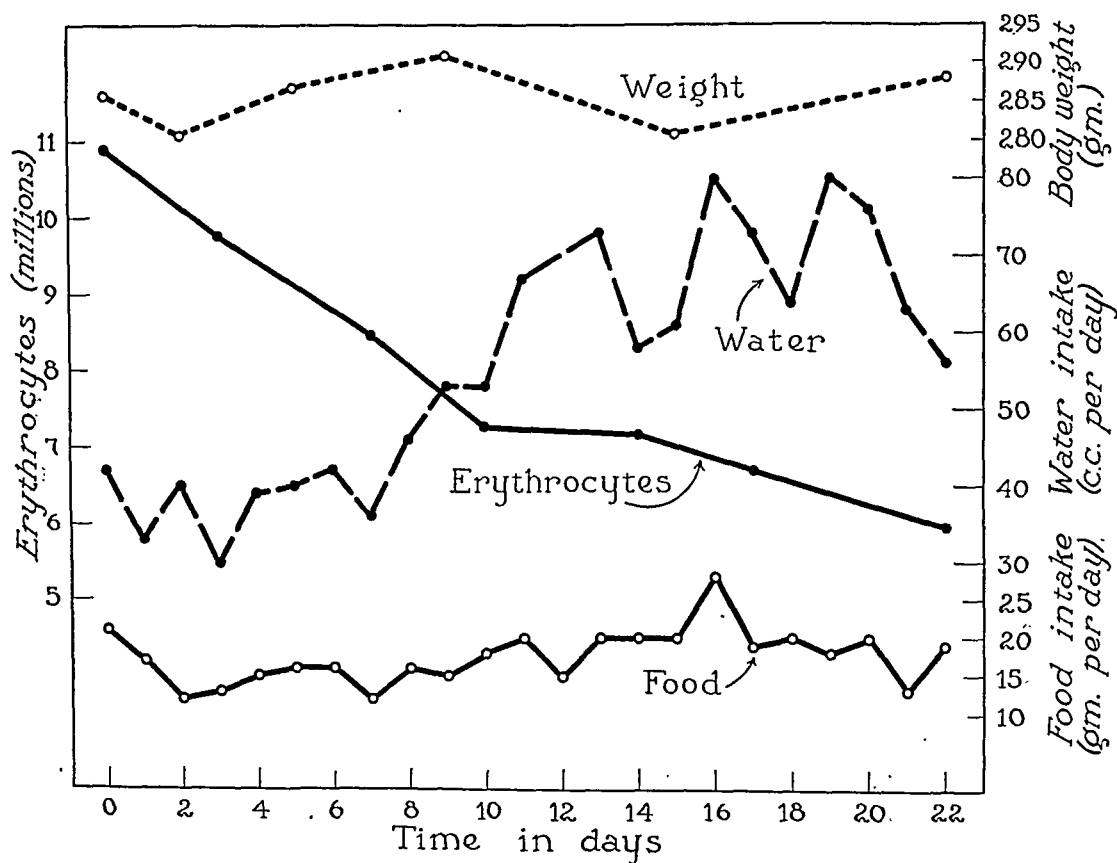


FIG. 2.—Increase in daily consumption of water which occurred simultaneously with a lessening of the degree of the severity of the anemia. No significant change occurred in food intake or body weight (average daily dose = 0.33 gm.).

the percentage drop from control levels was 3.9%, 16.9% and 38.5% respectively (Table 1).

Recovery From the Anemia. In order to determine whether or not recovery from the anemia and from toxic symptoms was possible following cessation of the administration of sulphaniilamide, the drug was administered daily to a group of 12 rats for a period of 10 days. The dose used was 2 gm. per kg. of body weight. The erythrocyte count dropped rapidly and was accompanied by similar

trends in the various erythroid components as was observed in the group which received doses of 1 gm. per kg. of body weight and as depicted in Figure 1. The erythrocyte level was lowest on the twelfth day, 2 days after discontinuing the drug. The continuation of the fall may be attributed to continued absorption of sulphanilamide still present in the distended stomachs of this group of rats (Fig. 5). A progressive macrocytosis, anisocytosis and a shift of the Price-Jones curve to the right developed as the anemia increased

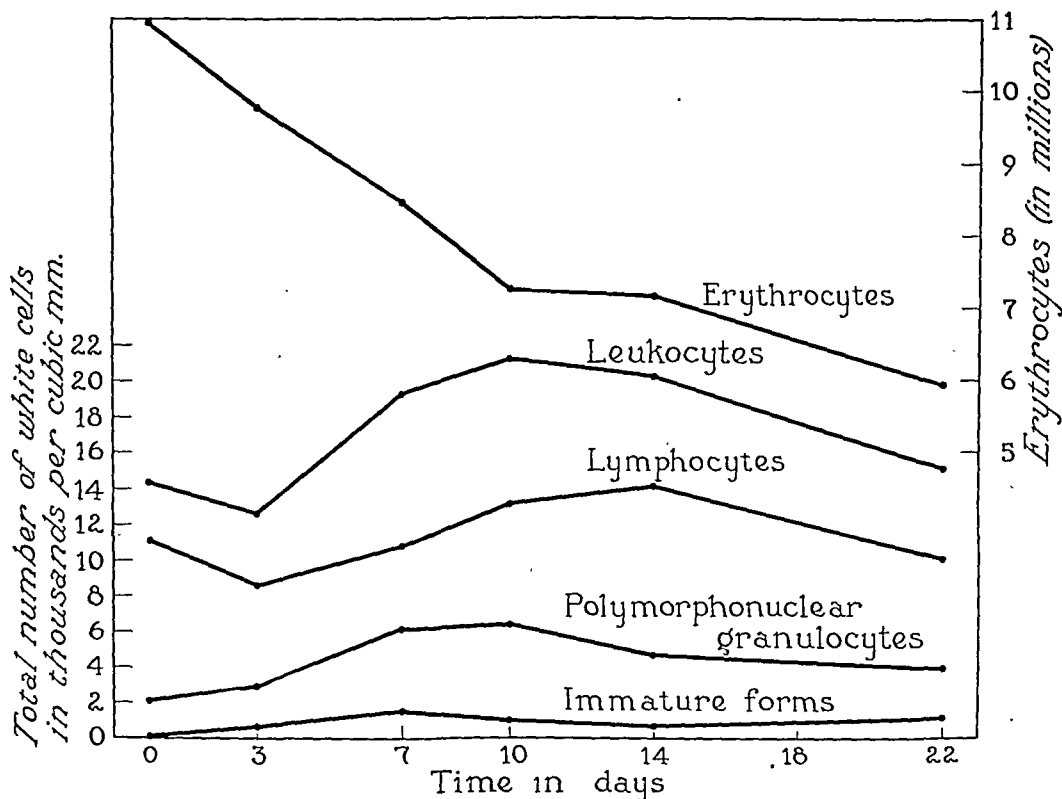


FIG. 3.—Trend in the myeloid elements of the peripheral blood in a group of rats receiving 1 gm. of sulphanilamide per kg. daily for a period of 21 days (average dose = 0.33 gm.).

(Fig. 6). Recovery from the anemia and from toxic symptoms, including weight loss, occurred gradually and was completed about 26 days after discontinuing the drug (Fig. 7). At this time the peak of the Price-Jones curve returned to where it had been during the control period (Fig. 6).

Effect of a Second Course of Sulphanilamide After Recovery From the First Course. Two months after the completion of administration of a course of sulphanilamide and about 1 month after recovery from the anemia thereby induced had occurred (Fig. 5), a second

course of the drug was administered to 2 of the animals daily for a period of 14 days. The dose used in both instances was 2 gm. per kg. of body weight. A fall in the erythrocyte level again developed which was very similar to that observed during the previous course of administration. Return of the erythrocyte level to the pre-administration level was completed by the twenty-fifth day after the drug had been discontinued (Table 2).

TABLE 2.—ERYTHROCYTE LEVELS DURING SECOND COURSE OF ADMINISTRATION OF SULPHANILAMIDE.

Time in days.		Erythrocytes (mills. per c.mm.).
Control		9.8
Period of daily ad- ministra- tion	2	10.0
	5	9.0
	7	7.2
	9	6.8
	12	6.6
	14	5.7
	17	6.8
Recovery	24	7.7
	30	8.3
	39	9.9

Toxic Manifestations Observed. Various toxic manifestations were observed in the animals which received sulphanilamide. These were most marked and most consistently obtained in the group which received doses of 2 gm. per kg. of body weight. These toxic manifestations included cyanosis, distended stomachs, irritability, drowsiness, weakness of the hind legs, convulsions, thirst and loss of weight.

Cyanosis was observed in all animals that received the 3 larger of the 4 dosages employed. This was manifested in the eye grounds, oral mucous membranes, tongue and feet. The blood of these animals had a peculiar violet-brown color, almost black. The onset of the cyanosis appeared to have no relation to the level of the erythrocyte count, some of the animals whose erythrocyte counts had as yet not fallen showing cyanosis. The appearance of the cyanosis occurred very early in the course of administration of the drug. Cyanosis has been reported in rats by Davis and his co-workers subsequent to the administration of sulphanilamide.

Convulsions observed in rats, mice and cats^{3,4,6,12} receiving sulphanilamide have been fully described in the literature. In the experiments which are the subject of this paper, in 8 of 54 animals to which sulphanilamide in various dosages had been administered convulsions developed. These occurred during the first 2 to 5 days of the treatment and developed about 2 to 4 hours after the drug had been given that day. They were observed only in the groups receiving the 2 larger dosages. The convulsions were of two types. In 6 of the animals, during the convulsive episode the animal lay on its side in a semicomatose state; the spine was arched dorsally, the head was thrown back and all four limbs alternately extended

and flexed in circular fashion somewhat similar to the motion of one's legs when propelling a bicycle. There was no significant rigidity of the limbs, which was in contrast to the type of convulsion observed in the remaining 2 animals. In the latter group, although the head was thrown back, the spine was arched ventrally and all four limbs were in rigid extension. There was a tendency on the part of the animal to attempt to rise into the air by tetanic spasms of the extremities. Two of the animals died during the convulsive seizures but the remainder recovered within 4 to 8 hours

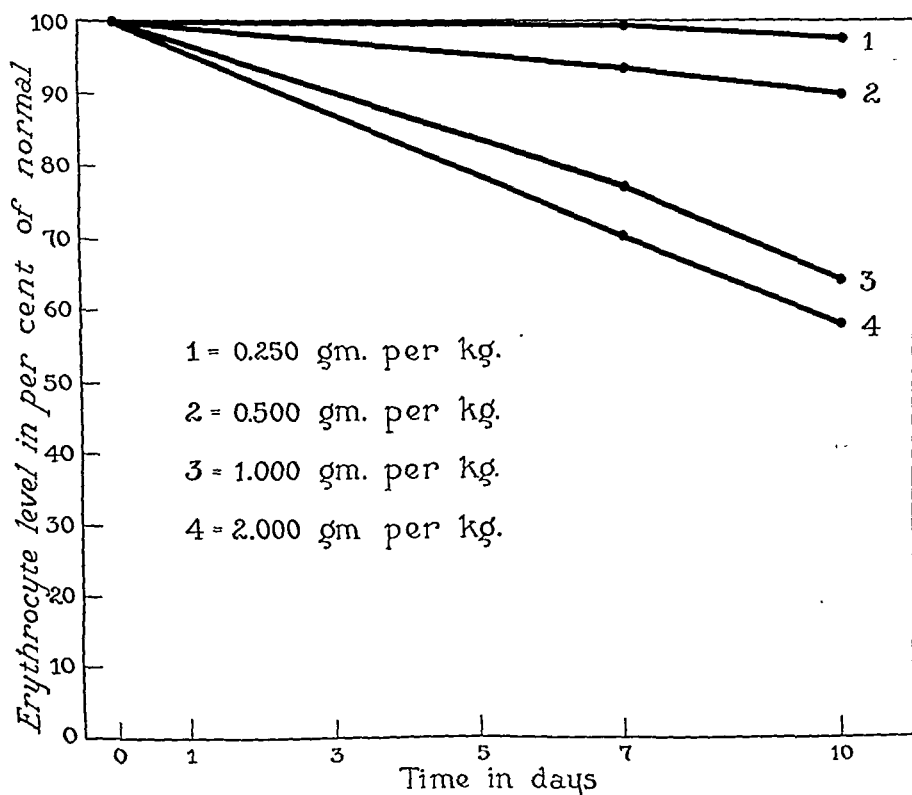


FIG. 4.—Percentage drop in the erythrocyte count from control level in four groups of rats on varied dosages administered daily for a period of 10 days.

after onset. In the group which recovered, convulsions did not recur despite the continued administration of the drug.

In most of the 24 animals to which the largest dose (2 gm. per kg.) of the drug was administered, huge abdominal masses gradually developed. These turned out to be stomachs distended with food and some retained sulphanilamide (Fig. 8). In 4 of 18 animals which received 1 gm. per kg. of body weight distended stomachs also developed. The distention in the latter group disappeared during the course of subsequent administration of the drug.

Loss of weight occurred only in the groups which received the largest dose. The animals regained this weight when administration of the drug was discontinued (Fig. 7). The loss of weight may be in large part attributed to the toxic, apathetic and helpless state of these animals and was accompanied by a concomitant decrease in food intake. No loss of weight was observed in the animals which received the 3 smaller dosages (Fig. 2).

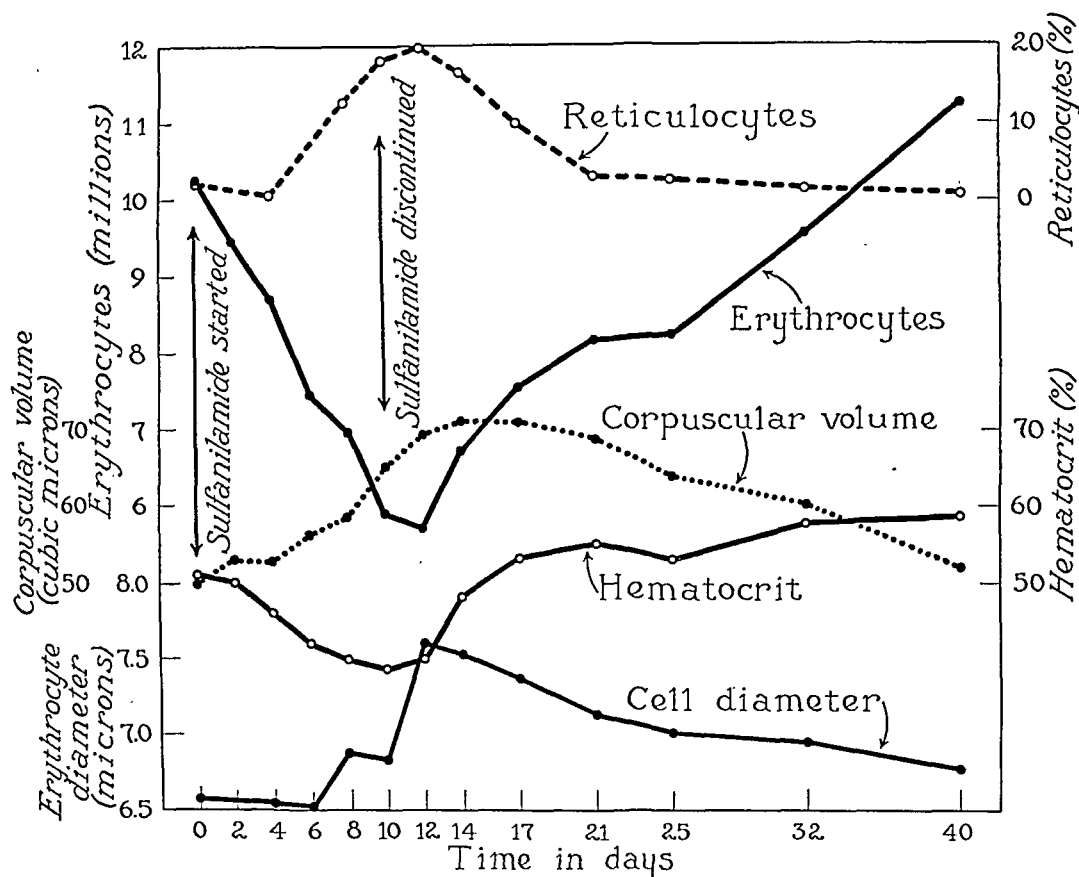


FIG. 5.—Trend of events in the erythroid elements of the peripheral blood in a group of 12 rats during the administration of drug daily for a period of 10 days and during recovery following cessation of administration. Dose = 2.0 gm. per kg. of body weight (average dose = 0.66 gm.).

During the course of administration of the doses of 1 gm. per kg., a marked thirst was observed to develop in the animals. In some of the groups a 100% increase in daily intake of water occurred during this period (Fig. 2) and was accompanied by a similar increase in the total volume of urine excreted. A similar occurrence was noted in one other of three groups studied on the same dosage.

In many of the animals a change in character of the stools developed. The stool, instead of being well formed and practically odorless, became semisolid and a strong pungent odor not unlike that of hydrogen sulphide developed.

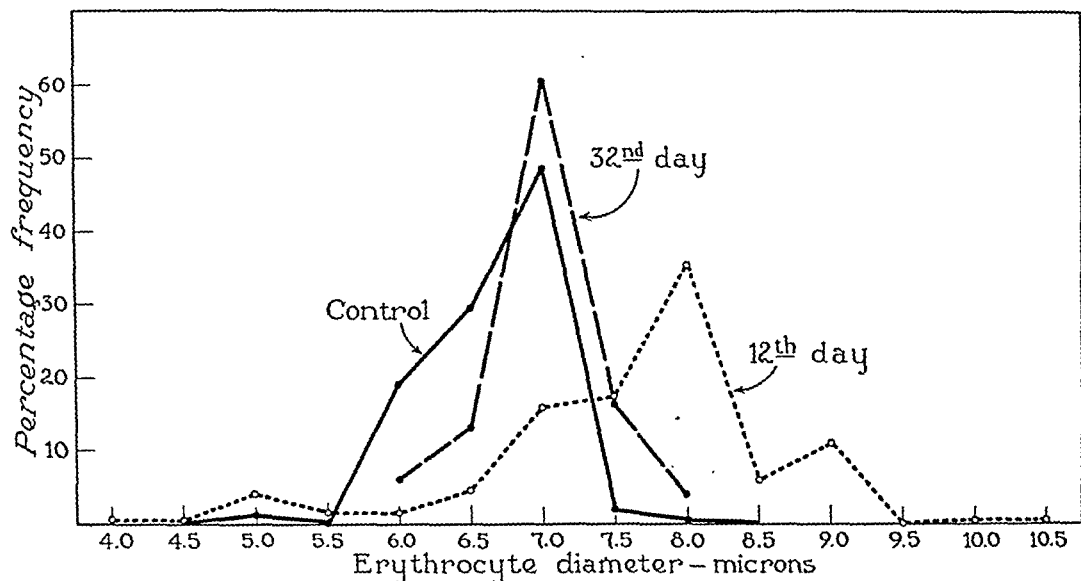


FIG. 6.—Price-Jones curves plotted during the control period, during the depression of the erythrocyte count and after recovery had occurred (32d day). The curve for the 12th day illustrates the anisocytosis and macrocytosis observed. Dose = 2.0 gm. per kg. of body weight.

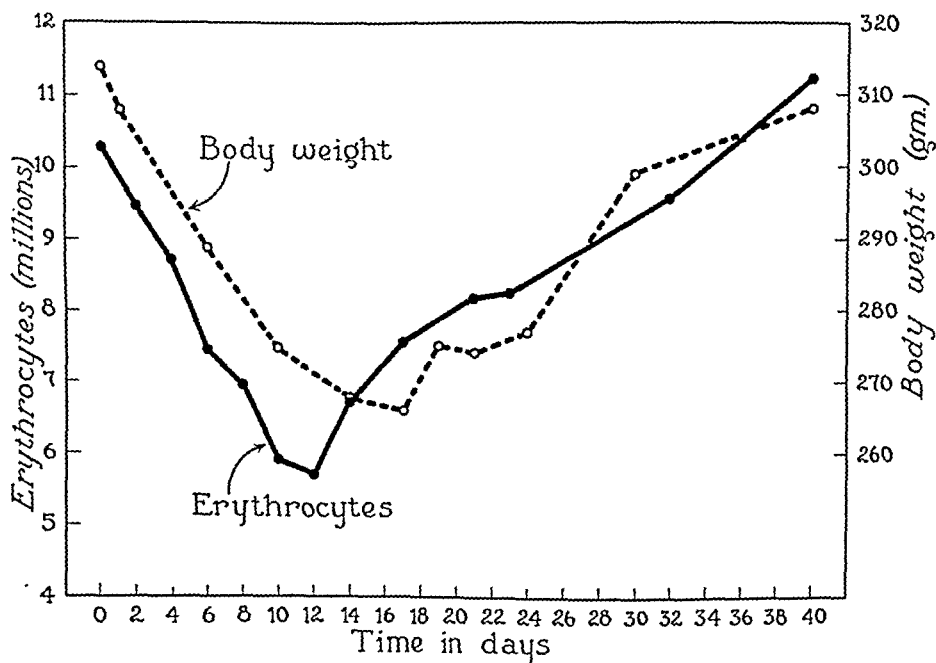


FIG. 7.—Trend in body weight and erythrocyte count during the development of anemia and recovery from it (2.0 gm. of sulphanilamide per kg. of body weight administered daily during the first 10 days).

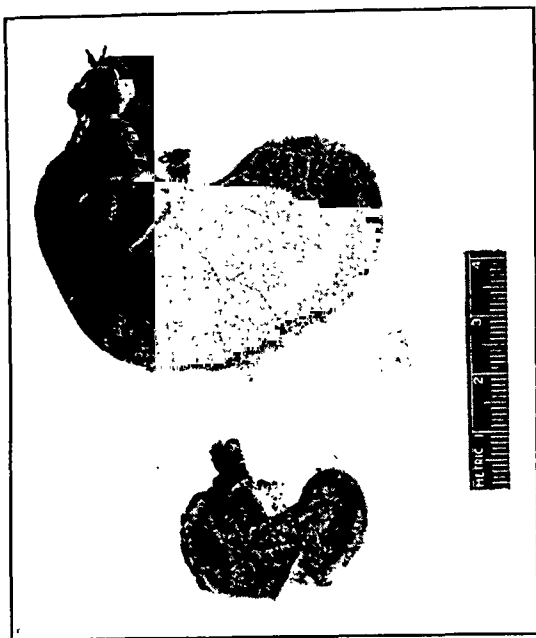


FIG. 8.—Stomach distended with food (upper) removed from animal that had received a daily dose of 2.0 gm. of sulphanilamide per kg. of body weight for 10 days. Lower stomach removed from control animal of same body weight. Both animals examined at necropsy at same time with respect to feeding.

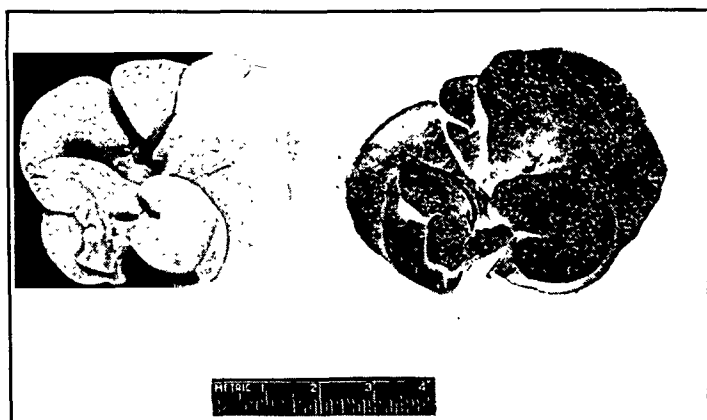


FIG. 9.—Liver on the right is from an animal which had received daily dose of 0.33 gm. of sulphanilamide over a period of 7 weeks. Body weight at necropsy was 290 gm., liver weight 13.675 gm. Liver on the left is from a control animal whose body weight was 300 gm., the weight of the liver was 9.475 gm. Note exaggerated lobular pattern in liver on the right.

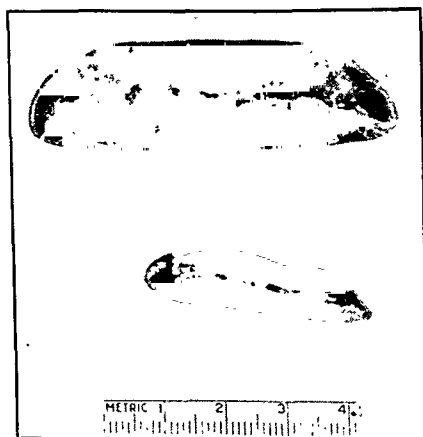


FIG. 10.—Spleens of animals whose livers are shown in Figure 9. The upper spleen weighed 5.140 gm., the lower spleen (from control animal) weighed 0.950 gm.

Clinical jaundice was not detected in these animals. Bilirubin was not found in the urine. Urobilin was found to be present in the urine but, since it was also found in the urine of control animals, it was rather difficult to evaluate this finding in view of the difficulties encountered in attempting to obtain samples of urine which had not been in contact with the feces of the animal. Epistaxis was not observed in any of these animals as was noted in the animals observed by Davis, Harris and Schmeisser.

Necropsy Findings. Animals were submitted to necropsy at regular intervals. Light etherization followed by decapitation was used as the method of preparing all animals, including controls, for necropsy.

Differences were observed in the necropsy findings between the groups which received the less and more toxic doses of sulphanilamide. Cyanosis and dark discoloration of vascular organs such as liver, spleen and kidneys were observed in all animals receiving the 3 larger doses. Enlarged lymph nodes, particularly in the splenic mesentery, were frequently observed.

In the group of rats which had received doses of 1 gm. per kg. of body weight, there was hepatomegaly and splenomegaly. The livers were firm, and had sharp edges and a smooth surface; frequently the lobular pattern was very noticeable (Fig. 9). The spleens were jet black in color and firm in consistency (Fig. 10). The degree of enlargement of the liver and spleen appeared to bear a direct relationship to the duration of the period of administration of the drug and to the degree of anemia at the time of necropsy (Table 3). In this group of animals fat was distributed in the abdominal depots in normal amounts.

TABLE 3.—RELATION OF DURATION OF ADMINISTRATION OF SULPHANILAMIDE AND DEGREE OF ANEMIA DEVELOPED TO THE WEIGHT OF LIVER AND SPLEEN.

Rat No.	Period of administration (wks.).	Weight in grams.			Per cent reduction in erythrocytes from control level.
		Body.	Liver.	Spleen.	
8SA	1	254	8.69	1.15	3.0
29SA	1	268	9.40	2.57	17.0
1SA	2	250	9.18	1.40	11.0
6SA	2	360	18.25	3.08	43.0
58SA	2	302	11.55	2.37	47.0
10SA	3	318	13.82	3.57	37.0
20SA	3	305	12.27	2.09	24.0
2SA	3	290	10.90	1.67	34.0
5SA	3	302	15.70	3.22	72.0
46SA	3	274	12.43	1.52	28.0
6SR	5	310	10.92	3.00	39.0
3SR	6	276	13.90	3.35	27.0
2SR	7	290	13.67	5.14	55.0
5SR	7	278	13.12	4.77	32.0
Controls*		298	9.60	1.14	

* Fourteen normal rats were necropsied as controls. Body weight ranged from 250 to 335 gm., average 298 gm. The liver weight varied from 8.100 to 10.400 gm., average 9.600; the weight of the spleen varied from 0.775 to 1.450 gm., average = 1.140 gm.

In the group which had received doses of 2 gm. per kg., the animals exhibited loss of weight and disappearance of fat from the abdominal depots. The stomachs were distended with food. All of these distended stomachs contained sulphanilamide retained from the administration of 24 hours before. There was frequently some dark blood on the surface of the antral mucosa; however, no gross blood could be detected in the small or large intestine. The femoral bone marrow in the experimental animals was hyperplastic.

A detailed report of the microscopic findings in the various organs and bone marrow will be published separately: in general, the microscopic findings are somewhat in accord with those reported in rats by Davis, Harris and Schmeisser.

Comment. Anemia can be produced in rats by the administration of sulphanilamide in adequate doses. Though the features of the peripheral blood of these anemic animals have a great deal in common with those in the acute hemolytic anemias reported clinically,^{5,11,15} which develop with an almost allergic-like suddenness, the anemia reported here, in its course, is one of the type referred to as occurring clinically in patients after prolonged administration of sulphanilamide,⁷ or in patients to whom the drug was administered and who had evidence of impairment of renal function.¹³ In the anemia induced in these rats, evidences in the peripheral blood are clean-cut for the fact that the bone marrow is not suppressed. Although it is strongly suspected that a hemolytic anemia was produced, the observations reported here cannot establish the suspicion definitely. Estimations of serum bilirubin have not been made. In view of the difficulties encountered in attempting to obtain samples of urine which had not come in contact with feces, the finding of urobilin in the urine of the control animals vitiates the significance of this finding in the experimental animals.

Conclusions. 1. Anemia can be induced in rats by the administration of sulphanilamide.

2. The degree of anemia depends on the dose used and the duration of administration.

3. The anemia is accompanied by evidences of stimulation of bone marrow, that is, reticulocytosis, macrocytosis, anisocytosis and leukocytosis.

4. No change in level of platelets has been detected.

5. Complete recovery from the anemia is possible following cessation of administration of the drug.

6. A second course of sulphanilamide will reproduce the anemia.

7. The drug is capable of producing toxic symptoms in rats, the symptoms depending on the dose employed. Symptoms include cyanosis, loss of weight, thirst, gastric distention, drowsiness, irritability and convulsions.

8. The anemia, when induced by moderately toxic doses, is associated with a significant hepatomegaly and splenomegaly.

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EPINEPHRINE IN OIL.

ITS EFFECTIVENESS IN THE SYMPTOMATIC TREATMENT OF BRONCHIAL ASTHMA.

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RECENTLY^{2,3} a suspension of powdered epinephrine in peanut oil was introduced as a slowly absorbed preparation of epinephrine. This suspension was so prepared that 1 cc. of oil contained 2 mg. of epinephrine. In an attempt to prove prolonged effectiveness for the epinephrine in oil it was administered to patients with chronic bronchial asthma, who had been taking for a period of months to years frequent daily injections or inhalations of epinephrine hydrochloride. With fewer injections of epinephrine in oil, these same patients had fewer attacks of asthma. The comparative effectiveness of epinephrine hydrochloride and epinephrine in oil was studied in patients with acute bronchial asthma, urticaria, and serum disease. In a similar manner, observations were made on the hyperglycemic and cardiovascular response. As the result of such studies, it was possible to conclude that a suspension of epinephrine in oil was slowly absorbed and possessed prolonged effectiveness. The remarkably good results obtained with epinephrine in oil coupled with the knowledge of its place in the medical armamentarium acted as stimulants for further study.

A change has been made in the technique of administration. It was formerly suggested² that dry sterilized syringes and needles should be used. The purpose of this was to conserve material put up in multiple dose packages by preventing contamination, and, therefore, oxidation of the epinephrine by water introduced from a syringe that had been sterilized by boiling. The epinephrine in oil

is now prepared in 1 cc. ampoules and the annoying technique of dry sterilizing may be abandoned. Epinephrine in oil is not harmed by the meager and transient contact with water in a syringe that has been boiled.

From the time studies were first begun until the present date, epinephrine in oil, accompanied by directions for its use and administration, was sent to interested physicians with the provisions that unbiased and accurate observations were to be made and submitted for compilation. The value of such multifarious data is inestimable. Therefore, the purpose of this report is to present further observations of my own along with those of other physicians on the effectiveness of epinephrine in oil in the symptomatic treatment of chronic and acute bronchial asthma. The data in this report were obtained by using epinephrine in oil that I and some of the pharmaceutical houses prepared. All the material was made identically and was equally effective.

Observations on Chronic Bronchial Asthma. The effectiveness of epinephrine in oil was studied on 11 patients with chronic bronchial asthma who had been taking injections or inhalations of epinephrine hydrochloride every 1 to 5 hours for a period of 2 months to 2 years. Of the 11 patients 7 were females and 4 were males. Their ages ranged from 31 to 78 years. It is important to emphasize that each patient received definite relief of symptoms, even though for short periods, from epinephrine hydrochloride. There is a small group of patients with chronic asthmatic symptoms who are not relieved by epinephrine hydrochloride and they, also, fail to respond to epinephrine in oil. This group of patients will not receive further consideration.

Three of the 11 patients were sick enough to be hospitalized. The 8 remaining patients were treated in my private office or in the out-patient department of the Johns Hopkins Hospital. The general scheme of treatment was identical for each patient.

Tolerance to epinephrine varies in different individuals and for this reason the first dose of epinephrine in oil was chosen cautiously. One cubic centimeter proved to be a safe initial dose for patients who were accustomed to frequent daily injections of epinephrine hydrochloride. Subsequently, the dose was either increased or decreased depending upon the response of each patient. Former studies² revealed that epinephrine in oil was effective for periods of 7 to 18 hours.

A total of 405 injections of epinephrine in oil were administered to the 11 patients. The number of consecutive injections administered to each patient ranged from 4 to 108. The dose of epinephrine in oil varied from 0.5 cc. to 1.25 cc. depending upon the individual requirements of each patient. The interval of freedom from asthma following one injection of epinephrine in oil ranged from 3 to 24 hours (Chart 1).

All the patients received injections regularly every night with the hope of preventing asthma long enough to permit adequate sleep and rest. If the patients were having asthma at the time when epinephrine in oil was to be administered, they were given beforehand an injection of epinephrine hydrochloride to give immediately relief of symptoms. Six of the patients did well with single evening injections and consequently their days became more comfortable. Four patients, however, continued to have their usual number of daily attacks and they were given an additional injection of epinephrine in oil in the mornings. One patient received a morn-

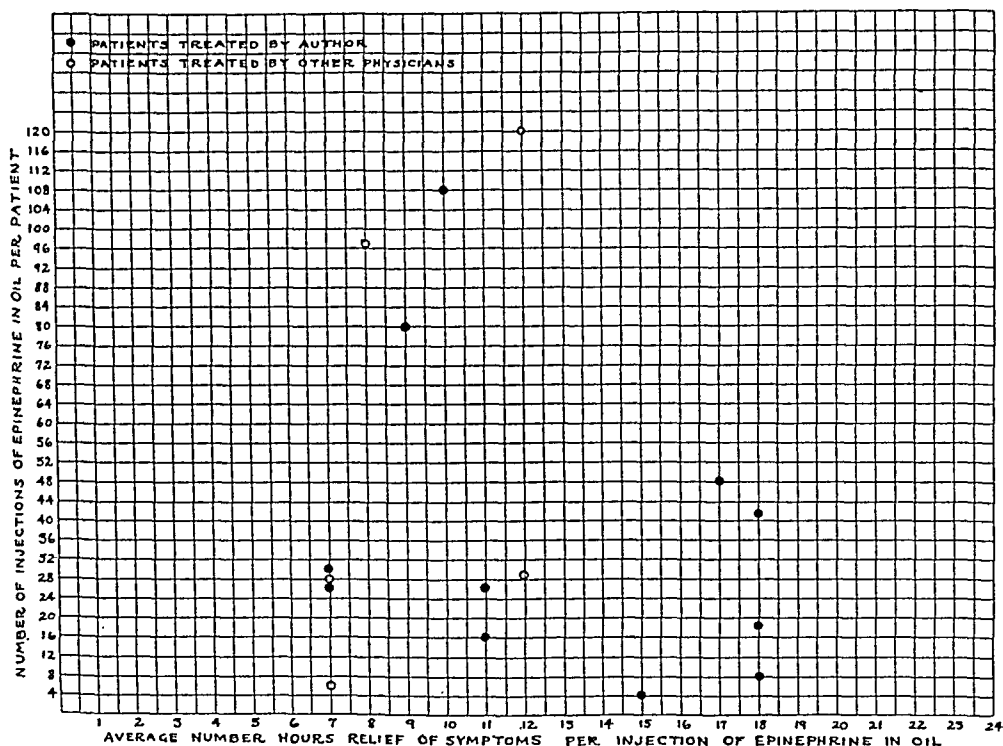


CHART 1.—Patients with chronic bronchial asthma. The dose of epinephrine in oil varied from 0.5 cc. to 1.5 cc.

ing, noon, and evening administration. Thus, it was possible, by beginning with a safe dose at a set time, by determining the effectiveness of the dose, by increasing or decreasing it according to the patient's response, and by supplying additional injections if necessary, to keep the majority of patients asymptomatic for long periods and eventually break up a vicious cycle of asthma which had existed for months.

There were few reactions to the oil. The 5 patients who had no local reactions at the sites of the injection had received 108, 48, 41, 18, and 8 consecutive administrations, respectively. Each of the remaining 6 patients complained of slight soreness at the sites of

injection for 12 to 24 hours. One of these 6 patients occasionally developed an area of localized redness and induration which persisted for 2 to 3 days. The incidence of local reactions decreased to a point of insignificance as soon as the material prepared by the pharmaceutical houses was made available. The injections were made either subcutaneously in the upper arm, or intramuscularly in the deltoid or gluteal muscles.

Only 1 serious reaction, referable to the epinephrine and manifested by the symptoms of shock, occurred from the 405 injections administered to the 11 patients. Subsequently, it became evident that the physician who had given the epinephrine in oil had made the injection through an 18-gauge needle. It is likely that small vessels were torn allowing the rapid absorption of the epinephrine. Large-gauge needles are conducive to rapid administration and it is logical to believe that the rapid introduction of an oily injectant might rupture small blood-vessels and thereby permit its rapid absorption. When epinephrine in oil therapy is indicated it is advisable to administer the material through a 23- or 25-gauge hypodermic needle.

Nine physicians submitted data on 10 patients with chronic bronchial asthma who had been taking frequent daily injections or inhalations of epinephrine hydrochloride for periods of 2 months to 4 years. Six of the patients were males and 4 were females. They ranged in age from 19 to 71 years.

Data on 7 of the patients included the exact number of consecutive injections of epinephrine in oil that each had received. The 7 patients received a total of 329 injections. The number of injections per patient ranged from 6 to 120. The dose of epinephrine in oil varied from 0.75 cc. to 1.5 cc. but 1 cc. was the usual dose. The interval of relief from symptoms following each administration of epinephrine in oil ranged from 4 to 20 hours, depending upon the severity of the asthma at the time the injection was given (Chart 1). Thus, the results obtained by these physicians are in accord with my own observations.

No mention was made by any of the physicians of reactions at the sites of injection and only on 2 occasions was attention called to minor side reactions referable to the epinephrine.

Observations on Acute Bronchial Asthma. The effectiveness of epinephrine in oil was studied during 1 or more acute paroxysms of asthma in 22 patients. The group consisted of 11 females and 11 males ranging in age from 6 to 49 years. The treatments with epinephrine in oil were administered in the out-patient department, on the public and private wards of the Johns Hopkins Hospital, in the patients' homes and in the author's private office. All the patients had been adequately studied and with the exception of a few all had been and were receiving specific desensitization therapy. The patients were asymptomatic most of the time, but occasionally

there was recurrence of asthma which could be traced to the onset of an upper respiratory infection or to the exposure to a specific pollen or inhalant to which they were sensitive.

One hundred and nine injections of epinephrine in oil were administered to the 22 patients during 40 different attacks of asthma. It was not always possible to compare the effectiveness of epinephrine in oil with that of epinephrine hydrochloride in the same attack of asthma. However, many of the patients had taken or had received epinephrine hydrochloride by inhalation or injection before epinephrine in oil was administered and were able to give an accurate account of the length of effectiveness of each preparation. In other patients it was possible to compare the effectiveness of epinephrine in oil with the effectiveness of other therapeutic measures in previous similar attacks. In general, the effect of epinephrine hydrochloride by injection or inhalation in the same attack or in previous similar attacks was apparent for only 1 to 4 hours. All the attacks were so severe that no beneficial response was obtained from adequate doses of ephedrine sulphate.

The dose of epinephrine in oil for each patient varied from 0.5 cc. to 1.5 cc. depending on the severity of the attack and on the age of the patient. In adults 1 cc. has been suggested² as an average dose for moderately severe asthma. This amount may either be increased or decreased depending upon the individual need of each patient. The dose for a child is naturally smaller. Usually, one-half to two-thirds of the calculated dose for an adult is safe and sufficient for a child between the ages of 5 to 14 years.

Inasmuch as epinephrine in oil is slowly absorbed, its effectiveness is delayed for a period of 15 to 30 minutes after its administration. Therefore, in 16 of the patients with moderately severe or severe asthma an injection of epinephrine hydrochloride was administered prior to that of epinephrine in oil to give immediately relief of symptoms. In a few patients several injections of epinephrine hydrochloride administered at 15-minute intervals, were necessary. Epinephrine in oil, because of its prolonged action, seemed to prevent the recurrence of asthmatic attacks and the results thus obtained were gratifying when compared to those of previous similar attacks where frequent injections of epinephrine hydrochloride had been necessary and where sleep had been interrupted because of recurring paroxysms of asthma. An injection of epinephrine in oil, alone, produced very good results in 6 patients with mild attacks of asthma. A single injection of epinephrine hydrochloride might have been equally as effective.

In 22 attacks of asthma the interval of freedom following the use of a combination of epinephrine hydrochloride and epinephrine in oil, or epinephrine in oil alone, varied from 6 to 24 hours (Chart 2). Eighteen of the 40 attacks were aborted with one injection. The length of effectiveness of the epinephrine in oil paralleled inversely

the severity of the asthma. In other words; when the asthma was severe the period of effectiveness for the epinephrine in oil was shorter. It was necessary to give morning and evening injections of epinephrine in oil to patients with persistent asthma. Only 1 patient failed to receive prolonged relief from adequate doses of epinephrine in oil.

Side reactions referable to epinephrine, such as nervousness or tachycardia, or both, were noted in 4 patients on 7 different occasions. These symptoms usually appeared 30 minutes after each injection and lasted for 1 to 2 hours.

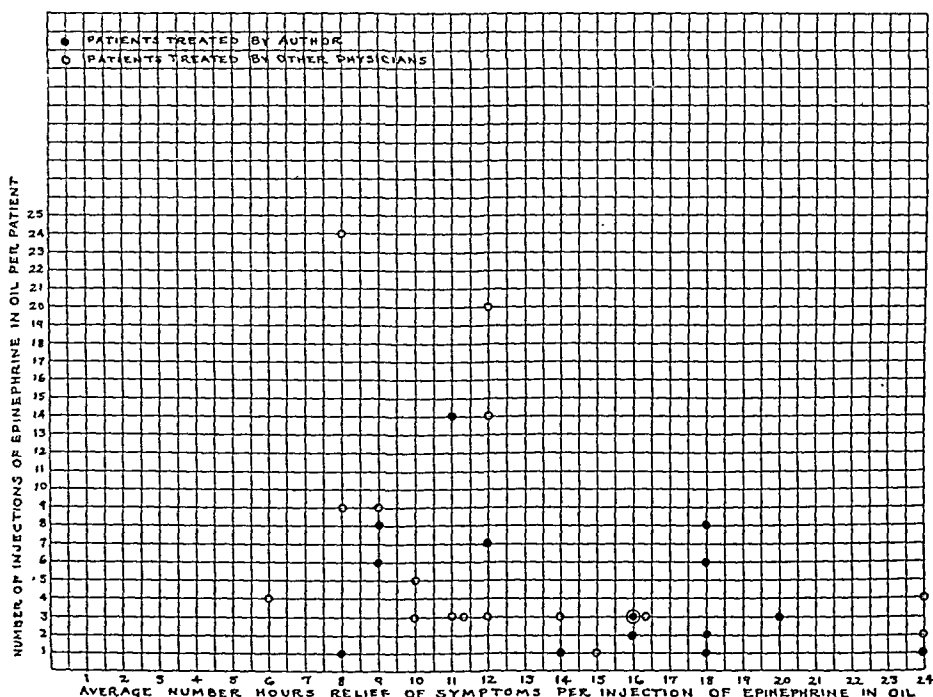


CHART 2.—Patients with acute bronchial asthma. The dose of epinephrine in oil varied from 0.5 cc. to 2 cc.

The injections were made subcutaneously in the upper arm or intramuscularly in the deltoid muscle. Six of the patients stated that the sites of injection remained tender for 1 or 2 days. This information, however, was obtained only by questioning the patients. One patient having received 2 injections without a local reaction, developed massive edema of the upper arm 24 hours following the third injection. It is likely that sensitization to peanut oil had developed. A skin test to the peanut extract was negative and there was no history suggesting peanut sensitivity.

Fourteen physicians reported on the treatment of 27 patients during 37 attacks of asthma. The group of patients consisted of 14 females and 13 males ranging in age from 17 to 63 years. Treat-

ment with epinephrine in oil was carried out in hospitals, in the patients' homes and in the private offices of the various physicians.

Twenty-two of the patients had been receiving epinephrine hydrochloride by injection or inhalation at frequent daily intervals for varying periods before the epinephrine in oil therapy was begun. No mention was made of the previous symptomatic therapy in 4 patients. One patient had been receiving several capsules of a proprietary medicine daily.

One hundred and twenty-four injections of epinephrine in oil were administered to the 27 patients. The dose of epinephrine in oil varied from 0.5 cc. to 2 cc. A dose of 1 cc. was most frequently employed. In 31 of the attacks the interval of freedom from asthma following the use of a combination of epinephrine hydrochloride and epinephrine in oil, or epinephrine in oil alone, ranged from 4 to 24 hours (Chart 2). Six of the 37 attacks were aborted. The results, therefore, were similar to my own.

Side reactions referable to epinephrine such as nervousness and tachycardia occurred only 4 times and only once was there mention of a local reaction at the site of injection.

Comment. Epinephrine hydrochloride is an effective therapeutic agent in treating symptomatically many allergic diseases. However, because it is rapidly absorbed, its effectiveness is evanescent. Since the isolation of epinephrine by Abel¹ many investigators have attempted to produce compounds with more prolonged activity by modifying the structure of the original epinephrine molecule. But the small size and lability of the molecule have prevented the accomplishment of such a goal. Epinephrine is insoluble in oil and for this reason, the physiologic activity and the integrity of its molecule are unaltered in such a vehicle. Recently^{2,3} it has been demonstrated that a suspension of powdered epinephrine in peanut oil, so prepared that 1 cc. of oil contains 2 mg. of epinephrine, is a slowly absorbed preparation of epinephrine that exhibits its activity over a long period of time. The addition of a slowly absorbed preparation of epinephrine to the medical armamentarium satisfies a need that has been apparent for many years.

Epinephrine in oil is now available to the medical profession in 1 cc. ampoules. As the powdered epinephrine is suspended in oil, the ampoules must be well shaken before the material is withdrawn. Epinephrine in oil may be injected subcutaneously in the upper arm, but if repeated consecutive administrations are to be made over a long period of time, it should be given intramuscularly in the deltoid or gluteal muscles.

Local reactions referable to the oil have been infrequent. Occasionally there have been complaints of slight soreness at the sites of injection. This type of reaction, which was insignificant as far as the patient was concerned, was probably produced by the fatty acids present in the oil.

There is no scientific proof that patients who are sensitive to

peanuts are in turn sensitive to peanut oil. Nevertheless, care should be exercised in administering epinephrine in oil to a patient that is known clinically to be sensitive to peanuts. It is not unlikely that sensitization to the oil itself might develop, but of the many patients treated and of the many injections made by myself and other physicians, only one reaction that might be so classified, has occurred.

The majority of the patients did not experience side reactions referable to the epinephrine. When nervousness and tachycardia appeared the ensuing dose was decreased to prevent the occurrence of such symptoms. One serious reaction for which there was adequate explanation occurred. Untoward reactions due to the rapid absorption of epinephrine can be prevented by administering the material slowly through a 23-gauge or 25-gauge needle.

Epinephrine in oil was administered to 21 patients with chronic bronchial asthma who had been taking frequent and regular injections of epinephrine hydrochloride every night and every day for periods of many months or years. With from 0.5 cc. to 1.5 cc. doses of epinephrine in oil, 20 of these same patients had fewer attacks of asthma and fewer injections. One patient failed to receive prolonged relief from adequate doses of epinephrine in oil. By giving morning and evening injections, or at times, morning, noon, and evening injections, the patients remained for the most part asymptomatic and very often the vicious cycle of asthma which had persisted for months was temporarily terminated. In the symptomatic treatment of severe chronic bronchial asthma, the dose and the time of the injection must be regulated to suit the individual need of each patient.

Forty-nine patients were treated during 1 or more acute paroxysms of bronchial asthma and each patient received from 0.5 cc. to 2 cc. of epinephrine in oil. Forty-eight patients remained free from asthma for 4 to 24 hours, but more generally for 12 hours. One patient received more satisfactory relief from epinephrine hydrochloride than from epinephrine in oil.

Because epinephrine in oil is slowly absorbed, its effect is not manifest until a period of 15 to 30 minutes has elapsed after its injection. Therefore, in the treatment of acute asthma an injection of epinephrine hydrochloride (1-1000) should be administered beforehand to relieve immediately the symptoms. In severe attacks of asthma several injections of epinephrine hydrochloride, administered at 15-minute intervals may be necessary to provide immediate relief. The results obtained by using a combination of epinephrine hydrochloride and epinephrine in oil have been remarkably gratifying. Finally, it is important to emphasize that if the patient is not benefited by epinephrine hydrochloride there is no need to administer epinephrine in oil.

Summary. Further studies are reported on the effectiveness of epinephrine in oil in the symptomatic treatment of chronic and acute

bronchial asthma. Reports of other physicians who have used epinephrine in oil in the treatment of chronic and acute bronchial asthma are compiled.

Twenty patients with chronic bronchial asthma who had been taking frequent injections or inhalations of epinephrine hydrochloride every day and every night for from 2 months to 4 years, received relief from asthmatic symptoms for from 3 to 24 hours with from 0.5 cc. to 1.5 cc. doses of epinephrine in oil. One patient received no prolonged effect from adequate doses.

Forty-nine patients were treated during one or more acute paroxysms of asthma and each received from 0.5 cc. to 2 cc. of epinephrine in oil. Forty-eight patients remained free from asthma for 4 to 24 hours. One patient received more satisfactory relief from epinephrine hydrochloride than from epinephrine in oil.

The injections of epinephrine in oil were made subcutaneously in the upper arm or intramuscularly in the deltoid or gluteal muscles. In all, 70 patients received 967 injections of epinephrine in oil. One severe reaction to the oil and one severe reaction referable to the epinephrine occurred.

Ten of the 21 patients with chronic bronchial asthma and 27 of the 49 patients with acute bronchial asthma were treated by physicians other than the author. The results of these various physicians were in accord with my own observations. Furthermore, the results, herein entered, aptly uphold observations reported in earlier publications on epinephrine in oil.

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CLINICAL EXPERIMENTS WITH MALE SEX HORMONES.

II. FURTHER OBSERVATIONS ON TESTOSTERONE PROPIONATE IN ADULT HYPOGONADISM, AND PRELIMINARY REPORT ON THE IMPLANTATION OF TESTOSTERONE.*

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THE evaluation of any therapeutic agent must ultimately be based on clinical observation. The effects produced in experimental animals can rarely be translated absolutely into terms of clinical

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response in man. The patient is therefore the final proving ground of a new drug, and clinical accomplishments the final yardstick whereby may be evaluated its effectiveness, indications, and contra-indications.

Testosterone is a new chemotherapeutic agent, developed through the combined researches of biologists and chemists in several countries, and now available for clinical use. A year ago we¹⁰ reviewed the literature up to date and reported our preliminary experience with the propionic acid ester of this compound in a small series of patients who suffered with hypogonadism. Therapeutic results at that time were very gratifying; and we concluded that, so far as our observations had gone, the drug seemed a complete substitution therapy for deficiency of the internal secretion of the testis. In that article we reviewed briefly also the long series of steps leading up to the final purification of testosterone, truly one of the greatest chapters in biochemical research.

In this paper we wish to report further observations on the use of this material in our original hypogonad patients, most of whom have been on continuous therapy for nearly 2 years; also the same uniformly excellent therapeutic response in an additional group of 16 adult hypogonad patients (some primary and some secondary hypogonadism), with a brief discussion of the present status of the drug and its future possibilities.

Hypogonadism is the result of deficiency of the internal secretion or secretions of the testis, and is manifested by varying degrees of developmental failure of the penis, scrotum, prostate, and seminal vesicles. There are other, sometimes striking, but less constant changes associated with testicular insufficiency, such as lack of development of body hair, failure of the voice to change, failure of the skin to attain adult appearance and texture. Depending on associated changes in other glands, heredity, age of onset of testicular deficiency and, perhaps, other unknown factors, there may be also obesity, overgrowth of the long bones with late closure of the epiphyses, lack of muscular development and strength, and genu valgum. There may be mental retardation, but more often there are marked secondary personality changes as a result of failure to develop normal physical attributes. All the characteristics of hypogonadism thus described may not be present in each individual, or to the same degree. In the diagnosis of hypogonadism the wide variation of normal limits must be recognized and appreciated. Usually textbooks state that puberty occurs between 11 and 13 years of age, occasionally as late as the 17th year. In general this is true, but one not infrequently encounters the advent of normal puberty before 11 years, and we have observed spontaneous pubescence as late as 19 years of age. Considerable further development of hirsuties has been noted in many males, even after the age of 25, and we have observed in some untreated hypogonad patients

slight deepening of the voice, growth of the beard, and so forth, between the ages of 20 and 30. Puberty and the normal variations of the foregoing attributes are, therefore, relative phenomena, and changes following treatment must be very critically evaluated.

In general, we have employed the same method of study as outlined in the previous publication,¹⁰ and have followed these patients objectively from both the general medical and the urological standpoints. At the same time we have attempted to evaluate as accurately as possible the subjective changes. We feel that in all these 22 patients the objective and subjective changes occurring during therapy were due to testosterone propionate and were not changes which might have occurred spontaneously.

In the past year reports have appeared from other clinics on series of hypogonad patients treated with injections of testosterone propionate.^{4,2,6} The results have been, in most respects, similar to ours. In most instances their patients have received more frequent injections of the material, though individual doses were of the same magnitude as received by our patients.

Further experiences with the use of testosterone propionate in 16 additional cases have not materially changed our original conclusions. In general, the following results have been observed from the use of testosterone propionate in typical cases of hypogonadism:

Erections are markedly increased, sometimes as early as the second day after beginning treatment. During the first 4 to 8 weeks erections may sometimes be so persistent and so firm, particularly in the morning, as to be painful; they occur frequently during the day. There is usually a diminution or leveling off of these excessive painful erections, and thereafter erections occur only normally, *i. e.*, in the morning or in response to the usual stimuli. Potentia has been developed in all patients who have attempted coitus, and many are sexually active for the first time in their lives. In all cases where there had been no ejaculation, this appeared subsequent to treatment. Nocturnal emissions have occurred in all cases, in most for the first time. In some patients, ejaculation has been accompanied by more pleasurable orgasm. The scrotum has enlarged and its skin, in most instances, has become more coarse, dark and redundant. Some patients have noted, soon after beginning treatment, a dragging sensation in the inguinal area, perineum and lower abdomen, but such sensations have disappeared after the first few weeks of therapy.

The penis has shown rapid enlargement in all diameters in most cases. We have accepted only the maximum extended length, measured from the peno-abdominal margin, for comparison, because of the inaccuracy of measurement of the flaccid penis, either in length or diameter. In some instances the penis is more than doubled in length. The amount of enlargement of this organ under therapy has apparently been dependent upon the development reached be-

fore the onset of hypogonadism. For example, in two instances in which hypogonadism began at about the age of 20, one from castration and the other from destruction of the pituitary, the phallic size was normal, and there has been no appreciable change in the size of the penis under therapy, although growth of the atrophic prostate and vesicles occurred with the reestablishment of complete potentia. The growth curve of the penis usually begins about the second week of therapy, the most rapid growth occurring during the first 4 months. Following this the rate of growth begins gradually to decline, and in the original patients who began treatment 2 years ago the growth of the penis is now at a standstill, though body hair continues to develop and complete functional ability is maintained. Thus penile growth under this form of therapy really mimics penile growth of normal adolescence.

The prostate and seminal vesicles have been stimulated to considerable growth in every case. These structures are probably the most sensitive indicators of androgenic activity. Complete adult development of the prostate has not quite been reached in most of our cases thus far. In some instances the consistency of the prostate under therapy has become normal, while in other patients the lateral lobes have not been as thick in the antero-posterior diameter and have felt somewhat softer than normal. In general, there has been rapid increase in size of the prostate so early after beginning injections that, to account for this, one might assume that one of the drug's most dramatic effects is rapid increase in the vascularity of this organ. The maximum growth rate of the prostate and seminal vesicles seems to be reached much sooner than in the penis, after which their size seems stationary, without further development, under similar therapy. The growth of the prostate and seminal vesicles is usually proportionate, and when slight variations in the growth of the two are present, it has been our impression that the rate of growth and ultimate size of the vesicles has been slightly greater than that of the prostate.

Prostatic massage has been carried out repeatedly in all patients and the resulting secretion studied microscopically. In all patients, prior to therapy, the secretion was either nil or extremely little and very thin. After therapy, in all instances, the prostatic secretion has not differed essentially from that of the normal adult. Some cases show abundant epithelial cells. In 2 patients after treatment the prostatic secretion appeared unusual, showing isolated and many conglomerate very large refractile globules. The amount of prostatic secretion seems to be in proportion to the palpable size of the gland.

Observations on the testes and epididymes have been carefully carried out in an effort to estimate any changes in their size and consistence. We have noted no decrease in size of the testes under treatment, and at times gained the impression that slight increase

has occurred. Some testes have seemed to become firmer; in other rare instances softer in consistency.

In many patients there has been immediate increase in body weight, but no consistent weight alterations have been noted. In some cases the weight gained during the first month of treatment has been lost subsequently. One patient has gained 21 pounds in the first 9 months of treatment. Some patients have shown no gain in weight whatever. Of 5 patients having obesity with hypogonadism, 2 showed a gain in weight while 1 did not change, 1 showed an actual small loss and the last showed an early gain of 15 pounds which was later lost. Gains in weight of 5 to 15 pounds were attained and held in all the non-obese patients. No dietary instructions were given these patients, and, so far as they were aware, their dietary habits did not alter during the periods of observation.

Change in the voice has occurred in those patients who had high-pitched, immature voices before beginning treatment. In other patients who had a more mature voice, there has been no change noted. The voice changes have occurred as early as the second week and as late as the third month after beginning therapy.

Objective and subjective changes in the breasts have been observed in several instances. This has consisted of tingling and painful sensations in one or both breasts, accompanied by hypersensitivity of the nipples to clothing. Neither the patients nor we have noted evidences of secretion. In approximately half of the patients having subjective breast changes we have been able to palpate irregular firm areas under the areolæ. In every instance breast changes have disappeared after the first several months of therapy.

There has been stimulation of the growth of hair in all patients. The rate of its growth depends somewhat on the amount of hair present before treatment is begun. The greatest growth has taken place in the pubic, scrotal and perineal regions. Pubic hair has proven a particularly sensitive indicator of effective therapy and has shown rapid and vigorous growth in all cases. Patients already having a small growth of hair over the lower abdomen have shown increased growth, with the male type of distribution. The site of the next greatest growth of hair is the axilla, then the lower legs, thighs and lastly the arms. In only 2 instances has there been marked increase in amount and stiffness of the beard; 1 of these patients was 39 years of age and had been castrated 20 years before. The other patient had marked hypogonadism secondary to the destruction of the pituitary gland by a cyst. Many other patients have stated they could discern slight increase in the fuzz on their chins and upper lips and this has been substantiated by our observations.

Patients with hypogonadism, particularly those underweight, have been described as having a progeric appearance, with skin of fine

texture and with many wrinkles, particularly around the eyes and corners of the mouth. The skin also has usually a dead, pasty appearance. We believe there has been considerable change in the skin of these patients, and this has been corroborated by their friends. One such patient says that he has been repeatedly told that his skin has a more youthful and healthy appearance, with better color. There has been uniform increase in secretion by the sebaceous glands of all patients, usually well manifest at the end of the first month of therapy. Acne has appeared on the face in 50% of the patients and persisted for varying periods of time, but never to any severe degree. One patient stated that before treatment he used to freckle when exposed to the sun, whereas since treatment he obtains a normal sunburn.

We have evidence to believe that added strength and energy with increased muscular development have accrued to several patients. This has varied from a marked degree in some to but slight increase in energy or drive in others. In every instance there has been most extraordinary improvement in the psychological outlook. They have acquired hope and become more cheerful, and each is highly desirous of continuing treatment. Especially interesting to us has been the psychological change in the little boy who was given the drug for other reasons than hypogonadism. In 1 year of therapy, 10 mg. having been administered 3 times a week, signs of sexual maturation appeared rapidly, with enlargement of the phallus and prostate and slight growth of body hair. During this period he showed unusual strength for his size and could climb in and out of a high bed. He was belligerent and completely overpowered the other children of his age on the ward. During the past year, since treatment has been stopped, his belligerent attitude has disappeared, and he now tends to be overconciliatory, thoughtful, and almost mother-like in his relations to the other children. The phallic size has regressed somewhat so that its extended length is now 9 cm., still larger than the average for his age. The scrotum is also larger and its corrugations are more prominent than those of other 6 year old boys. The prostate is no longer palpable, and no secretion is obtained from vigorous massage of this region. Testes are 1 cm. in length, which is the same as other children of the same age that we have examined; but the patient's testes are definitely smaller than they were at the end of his treatment.

In several adult patients whose bone age as determined by Roentgen ray examination was greatly retarded as compared with their actual age, repeated Roentgen rays after a year's therapy have not disclosed any stimulation to epiphyseal closure. McCullagh⁶ made the same observation in his treated patients. However, in the 3½-year-old boy just mentioned, the therapy over a year's time greatly advanced the bone age as judged by the appearance of the centers of ossification. His bone age at the present time is esti-

mated to be approximately 10 years, whereas his actual age is $5\frac{1}{2}$.* A similar observation was made by Webster¹¹ in his series of juvenile patients.

Optimal and Maintenance Dosage. The effects above noted have been obtained with subcutaneous or intramuscular injections of testosterone propionate in sesame oil. The dosage used was, with rare exceptions, 25 mg. given twice weekly. This dosage was arrived at arbitrarily. Because of the oily nature of the material we felt it wise not to allow self administration of the drug, and twice weekly was the maximum frequency at which our early patients found it possible to come for injections. Smaller doses given at this interval, *i. e.*, 5 mg., 10 or 15 mg., proved to bring about unsatisfactory responses. Twenty-five milligram doses brought about such satisfactory responses in our first patients that we have continued this dosage ever since, with the same happy results. Other investigators^{4,6} have treated patients with daily or almost daily injections of 25 mg. of the same material and obtained results essentially the same as ours. Since, in these similar groups of patients, 50 mg. a week given in two doses seems approximately as effective as 150 to 175 mg. given in divided doses, one gains the impression that there may be, by this method of administration, at least, a relative maximum effective dose beyond which little further result may be obtained. Since, with two doses per week, we were unable to obtain satisfactory effects with smaller doses than 25 mg., we feel the effective level to be somewhere in the neighborhood of 40 or 50 mg. per week in the adult type of hypogonad patient. However, there must be individual variability and age doubtless plays a rôle in the susceptibility to the hormone. As in other glandular deficiencies, the patient seems to be hypersensitive to the hormone he lacks, and we have interpreted in this wise the brief period of subjective over-stimulation noted in nearly all our hypogonad patients when first given testosterone propionate. Contrarily, the doses injected into these patients and even larger and more frequent injections could not be differentiated by normal healthy men from injections of plain sesame oil, and so far as these normal observers could tell, they obtained no subjective stimulation in the sexual or any other sphere. Nevertheless, a gain in weight with water and sodium chloride retention occurred in these normal subjects, as it did in the normal patient reported by Thorn⁸ and the eunuchoid patients reported by Kenyon.⁵ Also, in patients with impotence of psychiatric origin we have observed no response to the injection of the drug in any way comparable to the responses observed in hypogonad patients.⁷

Since the normal mechanism of the testis seems to be to extrude minute amounts of hormone at a fairly constant rate it seems likely

* We are indebted to Dr. Lawson Wilkins for these bone age determinations.
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that smaller doses than 50 mg. per week would be effective if given at much more frequent intervals. One of the patients in our series was so treated elsewhere before coming under our observation. He had been given daily injections of 5 mg. of testosterone propionate for slightly over 4 months, with effects which seemed to him almost as good as he later obtained from 25 mg. given twice weekly. We have thought that, theoretically at least, still smaller doses given 3 or 4 times a day would more closely approximate the manner in which the testes normally secrete their hormones into the general circulation. Experience thus far has convinced us that with injections of testosterone propionate given twice weekly it has been impossible to reduce the dose and still maintain full effects. We have tried, without the patient's knowledge, cutting the dosage to 10 mg. twice weekly, and within 2 weeks to a month, usually in the third week, there was complaint of some lessening of effect—such as absence of spontaneous morning erections, poor erections at coital attempts, absence of ejaculation. When we have substituted plain sesame oil for the usual 25 mg. of testosterone propionate twice weekly, the same complaints are registered, but much sooner—usually within 10 days to 2 weeks. We realize our conclusions thus far are based on subjective criteria which, as a general rule, are unsatisfactory; for, as will be seen later, the psychological quanta in the phenomena of sexual activity are very great. But the above-mentioned reduction in dosage was accomplished without any possibility of the patients' knowledge, and clinical response was uniform to such a degree that we believe these observations are valid. We have not as yet given any patient maximal effect by injections and then completely withdrawn therapy for prolonged periods in an effort to evaluate the objective effects of withdrawal. The longest withdrawal period was of 1 month's duration and only slight diminution in the size of the prostate was noted, though quite marked regressive changes had occurred in the scrotal skin, as called to our attention by the patient himself.

In summary, then, it has been our experience in patients who have been treated successfully with 25 mg. twice weekly, that this dosage cannot be much, if at all, reduced without subjective reduction in effectiveness. Contrariwise, no increase in tolerance to the drug when so given over 30 months has been noted. The significance of Kenyon's⁴ observation is not clear in the light of these experiences. He found in 1 patient successfully treated with 25 mg. daily and whose dosage was reduced later to 25 mg. twice weekly that "with the smaller dosage sexual stimulation was substantially below that of the previous high level." This, of course, might have been a psychological effect of the reduced number of injections. The power of suggestion in this field is a constant source of worry in interpreting subjective responses, as mentioned previously. An example may not be amiss at this point.

A 55-year-old technician, who has spent most of his life around medical clinics, was much impressed by reports of increased potentia resulting from the use of testosterone. He felt that his sexual powers over the past few years were waning, this constituting, so far as we could learn, an ability to have coitus only once an evening, whereas previously it could be accomplished twice or three times. He persuaded one of us to give him testosterone propionate in an endeavor to increase his sexual powers. A single injection of 50 mg. was given. The night after the injection he claimed to have had coitus three times and was delighted with the therapy. About a month later, having made plans for the following night, he asked us for a similar injection. Believing his previous medication to have been effective solely through suggestion, we administered 2 cc. of sterile sesame oil, having labelled each ampoule carefully and conspicuously with the usual label on vials of 25 mg. of testosterone propionate. The sterile oil injections produced the same marvelously satisfactory result as had 50 mg. of testosterone propionate. This experiment was repeated on several occasions with the same result, and it was interesting to hear the patient's statements that for several days after each injection of sterile oil he had so many spontaneous erections during the day as to seriously interfere with his work.

It is our opinion that several more years of clinical experiments with injections of the drug will be required before the optimal dosage for building up or maintenance effects can be ascertained. We feel that the experiences we have had thus far yield only suggestive evidence in this regard.

The following case report is representative of the results which we have observed in hypogonad patients when given testosterone propionate injections in 25 mg. doses on an average of twice weekly. Through a mistake this patient was given an injection 3 times per week for the first 2 weeks, but otherwise his story is entirely representative of the group as a whole.

W. P. A., B. U. I. 26769, aged 27 years, was admitted March 26, 1938, complaining of failure of the penis and testes to develop. He gave a history of bilateral cryptorchidopexy at the age of 11, after which there was no further sexual development. There were occasional, well sustained erections with some sexual desire, resulting in occasional masturbation with some sensation and the appearance of a tiny amount of fluid at the meatus. There were no hot flushes. He was nervous, self-conscious, and stated he took particular pains to conceal his genital underdevelopment. He had received several courses of pregnancy urine principle and orchidic substances without change except, he believed, there was some slight development of hair about the genitalia. He shaved twice a month. He stated his voice had become slightly lower-pitched during the past 3 years, but his co-workers often jested about his sissy voice.

Examination. The patient was a tall, eunuchoid individual with disproportionately long arms and legs (Fig. 1A). Height 6 feet, 2 inches, weight 150 pounds. There were long scars in both groins, the result of previous operation. Genitalia: The penis was small (Fig. 2A), about 2 cm. wide, and on extreme traction 8.5 cm. long. The scrotum was very small and underdeveloped. Both testes could be palpated just below the external rings, the right measuring about 5 to 6 mm., the left distinctly smaller. Rectal examination: Anal sphincter of average tone. Perineal muscles apparently of normal development. Prostate very indefinite, but one got the impression that there was perhaps a very small amount of lateral lobe

tissue a little over 1 cm. wide around the urethra (Fig. 3A). Membranous urethra normal. One could palpate two cords in the position of the ampullæ; these were taken to be terminal vasa. The impression of small, soft structures adjacent to these was obtained and though indefinite, these were taken

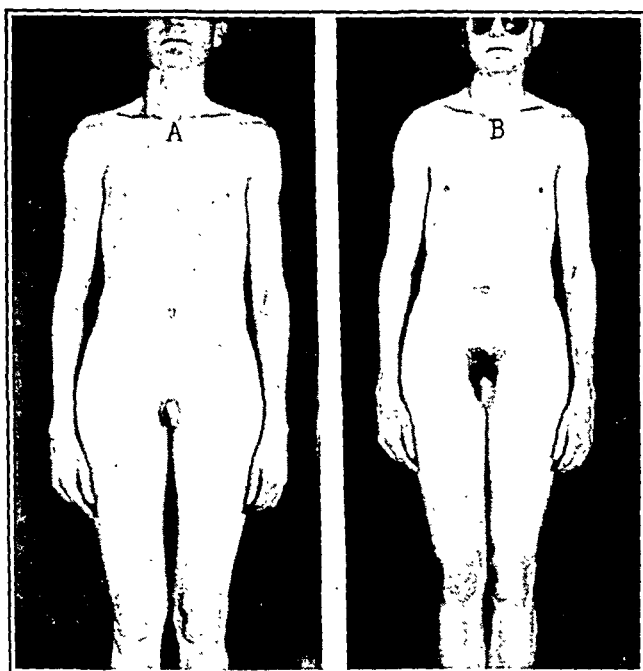


FIG. 1.—A, Patient (aged 27 years) before treatment. B, Same patient after 11 months of therapy.

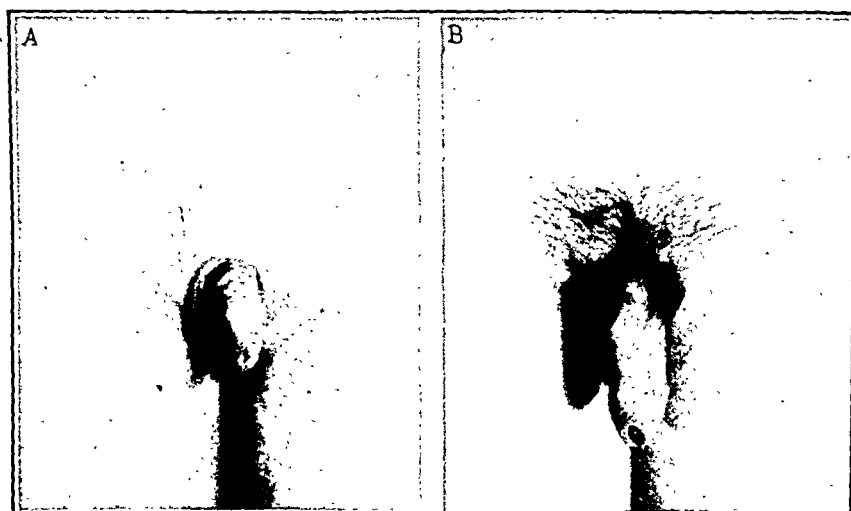


FIG. 2.—A, Genitalia before treatment. B, Genitalia after 11 months of therapy.

to be minute seminal vesicles. No prostatic secretion could be expressed on vigorous palpation. The body hair development was considerably retarded. There were about a half-dozen black hairs on either side of the pubic area (Fig. 2A), as well as in the axillæ, and a few dark hairs on the anterior portion of the scrotum. There was an indefinite, fine fuzz present on the chin. No hairs on abdomen. There were short, dark, sparse, fine hairs on the forearms and lower legs. There was no palpable breast tissue. There was marked retardation of bone age as determined by Roentgen ray. Urinary prolan was present in a concentration of more than 50 and less than 100 rat units per liter. Roentgen ray of the sella turcica was normal. *Endoscopy*: No. 16 McCarthy cystoscope passed with some difficulty because of narrowness of the urethra. Bladder mucosa and vesical orifice normal. Coming back into the urethra, the urethra fell together from each side, giving the appearance of two lateral lobes with slight corresponding clefts at the vesical orifice. The floor of the urethra distal to the vesical orifice was raised, with bullous edema being present. No verumontanum could be localized in this somewhat bullous area. Ejaculatory ducts could not be visualized. Remainder of urethra normal; no evidence of vaginal orifice.

Treatment: April 5, 1938, testosterone propionate, 25 mg. per dose, was begun and given every other day for 5 doses. After the first injection he noted a distinct change in the scrotum which became more lax and loose. During the first 10 days when he had injections every other day there were erections a large part of the time, with almost continuous erection at night. No seminal emissions and no masturbation. During these 10 days there was a gain of 10 pounds in body weight. At the end of this period there was definite distention of a tiny prostate and a drop of secretion was obtained. After April 16, 1938, the patient received 25 mg. of testosterone propionate twice weekly for a year. After the seventh injection the voice began to crack, the nipples became slightly sore, but without secretion. At the end of the first month he complained of intense libido and indulged in frequent masturbation. There was the appearance of an ejaculate within the first month of therapy. The skin of the face and neck had definitely become darker. He claimed that his joints were stiff, though he had taken no unusual exercise. At the end of the first month there appeared under each nipple a small area about 2 cm. in diameter, of firm breast tissue, without any secretion. At the end of this month the penis had grown $1\frac{1}{2}$ cm. in extended length. The prostate was then about one-fifth normal size, soft and succulent. Seminal vesicles distinctly palpable. The erections which had previously amounted almost to priapism had begun to decrease somewhat in intensity. Between the middle of May and the middle of June, when he was seen again, the voice had become definitely deep, the breasts had become less tender, though the nodules were still present. He now weighed 166 pounds. There was distinct growth in pubic hair and the penis now measured 10.4 cm. in extended length. A distinct growth of hair had appeared over lower legs. Prostate was now one-half normal size, of normal contour, as were the seminal vesicles, and the prostatic secretion was normal. He returned September 3, still having frequent erections during the night, in the morning, and several times during the day. He was masturbating more than once a week, with a considerable quantity of ejaculate. The nodules in the breasts had disappeared. Weight was now 170 pounds. He was distinctly more masculine in appearance, stronger, and obviously more muscular than before treatment. The penis was 11.2 cm. in length and undoubtedly greater in circumference. The scrotum was more redundant but there was no change in the testes. The prostate and seminal vesicles were about one-half normal size, with considerable secretion. The voice was quite deep, and he stated that cracking no longer was present. By the middle of October, pubic hair was becoming quite profuse,

as was the hair on the lower legs. The patient was now having frequent coitus, sometimes 3 or 4 times a night, with firm, well-sustained erections, normal ejaculations and orgasm. Figures 1 and 2 show the patient before and after 11 months' treatment, during which time he received approximately 2400 mg. of testosterone propionate. The prostate and seminal vesicles were now of normal size (Fig. 3B), the prostatic secretion normal in amount and on microscopic examination. On March 4, 1939, two pellets of crystalline testosterone were inserted into the arm. April 22 he returned, stating he was having even more erections following the implantation of the pellets, with just as much potentia and no change in orgasm or ejaculation. On April 22, 1939, the skin incision was opened and the pellets removed, weighed, and another pellet was reinserted. It was found that during the interval he had absorbed an average of 4 mg. a day of testosterone. Maintenance, as judged subjectively by him, was entirely comparable to that produced by doses of 25 mg. of testosterone propionate injected twice weekly. There was distinct continued growth of pubic and body hair during this time. The penis now measured 14 cm. in length and 3.2 cm. in width. Thick hair was developing under the arms and the patient now had to shave once a week. No breast tissue was palpable. The prostate remained entirely normal in size, shape and consistency, as did the seminal vesicles, with a large amount of secretion being expressed on palpation.

Implantation of Pellets. The effects above reported in hypogonad patients, resulting from injections of testosterone propionate in oil, seem to us adequate and entirely satisfactory replacement therapy. But the mode of administration leaves much to be desired; because of its oily nature we have felt it wise for the injections to be performed by physicians, and two trips per week to a physician's office for life is rather a strenuous program to anticipate. No peroral therapy of similar therapeutic potentialities has yet been developed. Two years ago the extraordinary effectiveness of pellets of crystalline hormones implanted beneath the skin of birds was reported by Deansley and Parkes.¹ Because it seemed likely that testes normally function by giving off more or less constantly minute quantities of androgens, the pellet method seemed to us extraordinarily adaptable for androgenic therapy. Consequently, we began trials with compressed tablets of testosterone placed in the subcutaneous tissues of our patients, in the fall of 1937. Because the tiny pellets of estrogens seemed equally effective as quite large injections of that substance in oily solutions, we tried at first using very minute pellets of testosterone placed subcutaneously by way of hypodermic needles. Pellets were made, each weighing approximately 2 to 3 mg.* Six to 30 mg. were injected at one time. Patients were used for testing who had shown the usual excellent therapeutic response to injections of 25 mg. of the oily solution twice weekly. No therapeutic effects of the pellets were observable, and withdrawal symptoms were noted in each instance in brief periods of time.

Following the work of Thorn,² who found that in adrenalectomized dogs pellets of desoxycorticosterone were required which would

* These pellets were kindly made for us by Dr. Carl Hartman of the Department of Embryology of the Carnegie Institution of Washington.

yield approximately 3 mg. into the circulation daily for a good maintenance effect, we began last year to use much larger pellets of 100 to 800 mg. each of testosterone, implanted beneath the skin. Excellent therapeutic results have followed this procedure in every instance thus far. We are at present studying 10 hypogonad patients on pellets placed in the subcutaneous tissue surgically, and following the objective and subjective clinical effects together with periodic assays of urinary androgen excretion.³ The pellets are removed and replaced at regular intervals in an effort to ascertain the amount of their substance given off per unit of time, the consequent duration of their effect; and thus we hope to determine the frequency with which they need be renewed.

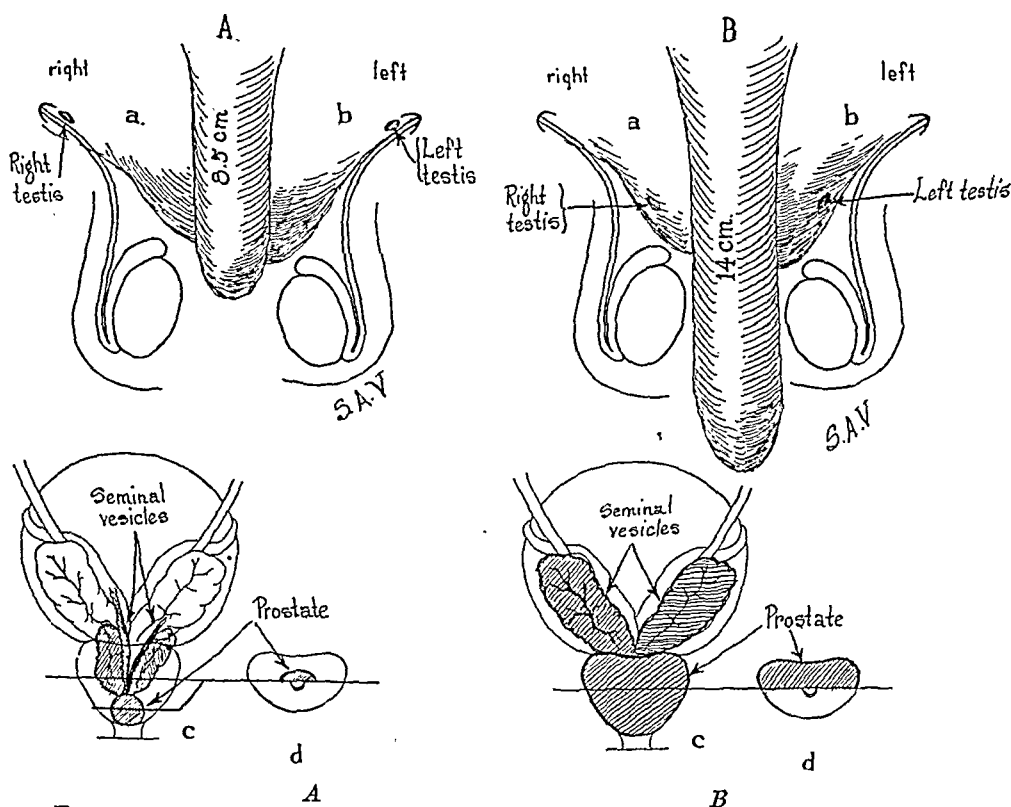


FIG. 3.—A, External and internal genitalia before treatment. B, External and internal genitalia after 11 months of therapy.

All patients who have thus far been transferred from injection to pellet therapy have reported enthusiastic and gratifying results. It is, as yet, too soon to determine whether pellets will be disintegrated with uniform rapidity in all patients, and one would guess that this probably would not be so. No patients have, thus far, reported over-stimulation effects.

One patient has impressed us particularly: A 64-year-old eunuch (Case 5 of first paper) had severe vasomotor symptoms following castration, only partially relieved by injections of 25 mg. of testosterone propionate twice

weekly. He was still having 10 to 20 flushes daily and drenching sweats, despite complete restoration of libido and potentia with bi-weekly injections. The implantation of one large pellet of pure testosterone (Fig. 4) subcutaneously reduced to negligible proportions the flushes and sweats, at the same time maintaining libido and potentia at a level at least as satisfactory as the injections of testosterone propionate had done. Strangely enough, the excess excretion of urinary prolan did not alter despite the great symptomatic improvement. This patient had been, on several occasions, tested with reduction in injected dosages and also with injections of plain sesame oil, always with prompt symptomatic decline. There seems little doubt that the pellet therapy has, in his case, been greatly superior. As he himself expresses it, "The pills are much better because they keep my sex life just as good and have saved my life by getting rid of those plaguing sweats and flushes." For a period of 75 days these effects were maintained.

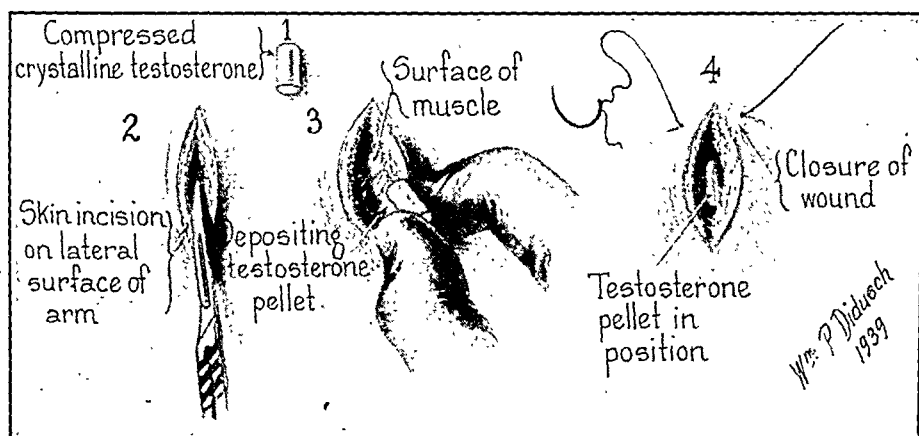


FIG. 4.—Technique of pellet implantation.

Equally efficacious have been the therapeutic results in other patients in whom pellets of the larger size have been implanted. Thus far, we have in most instances used pellets of pure testosterone crystals. It is possible that in the future other forms of testosterone or chemical variants of this compound may be utilized, with even greater or more economical clinical effects. We have implanted in monkeys and hypogonad patients pellets of other esters of testosterone and observations are at present in progress. Perhaps a peroral preparation will be prepared which will be clinically effective.

Summary and Conclusions. Observations extending over a period of 2 years on the effects of testosterone propionate in sesame oil given by hypodermic injections to 22 adult patients suffering from hypogonadism are reported. Development or reestablishment of secondary sexual characteristics with induction of normal libido and potentia have been observed. The dosage for maintenance and optimal therapy is discussed; and in our experience 2 doses per week of 25 mg. each has seemed adequate. Smaller doses, if given more frequently, seem equally effective, but if injections are given only

twice weekly smaller doses than 25 mg. proved inadequate for good therapeutic results. A preliminary report is given on the surgical implantation of compressed pellets of pure testosterone. Results thus far are encouraging and have seemed equally efficacious as those resulting from injections, far less troublesome to the patients, and somewhat sparing of material.

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EVALUATION OF VITAMIN B₁ (THIAMIN CHLORIDE) IN THE TREATMENT OF POLYNEURITIS.*

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THE development of the idea that there is a close interrelation between polyneuritis and vitamin deficiency has taken place within a short space of time. In the East, the interest in polyneuritis arose from the prevalence of beriberi and in the West, the ever present group of alcoholics afforded ample material for the study of the same clinical entity. Accident, deductive reasoning and experimentation in both parts of the world have brought about the evolution of the concept that avitaminosis is intimately linked with all types of polyneuritis.

In 1897, Eijkman¹ observed beriberi in some chickens accidentally confined in his laboratory and proved by subsequent studies that changes in diet could cause or prevent avian polyneuritis. In 1911, Funk² demonstrated that the beriberi-preventing factor in the diet contained nitrogen and to this substance he gave the name "vitamine."

Kimura⁵ in 1913 first reported the fact that pathological examination revealed identical changes in the nerve trunks in cases of beriberi and in cases of alcoholic polyneuritis. The clinical significance of these early studies seemed to pass unrecognized for many years. In 1928 Shattuck⁷ stated that it seemed logical to assume a similarity

* Read before the Section of Medicine, The New York Academy of Medicine, Tuesday, November 15, 1938.

between the polyneuritis of beriberi and all the other forms of polyneuritis. He expressed his belief that vitamin B deficiency plays a rôle in all such cases and urged that the therapeutic test be applied to patients with polyneuritis.

In the decade that has since passed, Shattuck's theory has been proven correct by many workers. Wechsler⁹ in 1933 reported improvement in alcoholic polyneuritis by a vitamin rich diet and he maintained that alcoholic polyneuritis as well as the neuritis of pregnancy were due to lack of vitamin. Later experiments by Minot⁶ and his group and by Jolliffe^{3,4} and his associates confirmed these observations.

During these years Williams¹² and his co-workers were improving the concentration of their yield of vitamin B₁ and experimental feedings of these concentrates to cases of polyneuritis was begun in 1933. In a short time Williams^{10,11a,b} made available pure crystalline material which was used instead of the concentrates and since 1936 the synthetic vitamin—now tentatively called thiamin—has been employed.

Following the preliminary report⁸ of the first 100 cases in 1934, continued observations in a larger group of cases of polyneuritis have been made. Since 1934 many hundred workers have corroborated the beneficial results reported in the first 100 cases. Today there seems to be little doubt that vitamin B₁ is of value therapeutically in polyneuritis.

The cases in this series were classified as cases of polyneuritis based upon the following diagnostic criteria:

1. Recurrent attacks of pain occurred with typical peripheral nerve distribution in more than one area of the body.
2. All cases complained of pain for longer than 1 month and had one or more recurrences since the initial attack.
3. All cases complained of paresthesias, weakness, and diminution of muscular power in the affected regions.
4. Neuromuscular tenderness (Valleix's Points) were present in all patients.

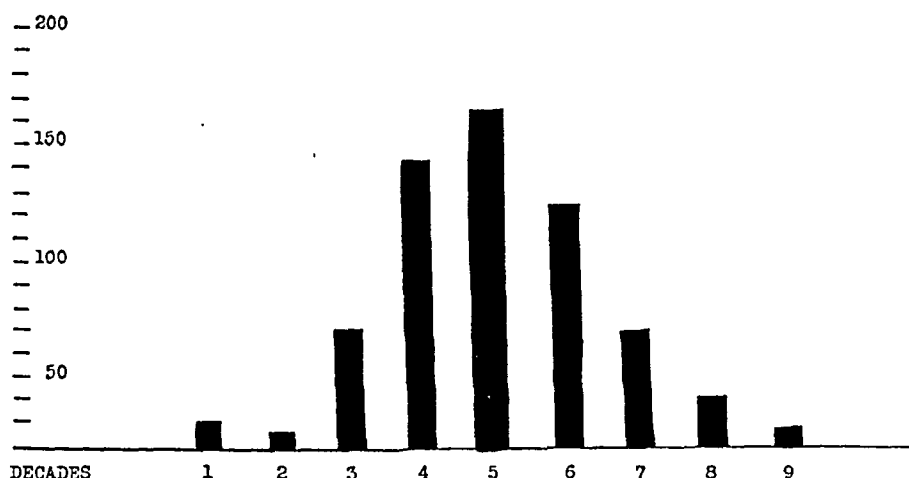
5. Reflex changes, either exaggeration, diminution or loss of reflexes and reduction in vibratory perception, were noted in all cases.

In view of the varied etiology present in this group the designation of these cases might be more accurately "Multiple Neuropathy" but the more usual term of "Polyneuritis" has been employed for clinical simplification.

In the treatment of these patients, pure vitamin B₁—at first the natural product and later the synthetic material—was the only therapeutic agent used. No change in the diet of these cases was made. In about 75% of the cases, thiamin was given orally and in the remaining 25%, parenterally. The relative merits of the oral and the parenteral method of thiamin administration will not be discussed; both are of value and each has its disadvantages.

In this series of patients the daily dose of thiamin varied considerably and was determined by the duration and severity of the polyneuritis and modified according to the clinical response. The average daily dose of thiamin chloride for the entire series ranged from 3 to 10 mg.; *i. e.*, from about 1000 to 3000 international units daily. Large doses were used routinely and usually given parenterally where no improvement was noted and to those patients whose response was either slow or incomplete.

TABLE 1.—DISTRIBUTION BY DECADES OF 520 CASES OF POLYNEURITIS TREATED WITH THIAMIN.



This report is based upon a study of 520 patients of whom about 60% were female and about 40% male. The age of these cases varies from the first to the ninth decades of life but over 72% occurred from ages 30 to 59. In those patients who responded favorably to the administration of thiamin chloride there was a considerable variation in the duration of time before improvement was noted.

TABLE 2.—ETIOLOGIC FACTORS IN 520 CASES OF POLYNEURITIS TREATED WITH THIAMIN.

	No.	%.
Toxic—heavy metal	5	1
Toxic—endogenous	26	5
Gestational	12	2
Metabolic	118	20
Nutritional	125	22
Infectious	161	29
(?)	115	20
Total	562	

This factor of the length of time elapsed before the beginning of response to treatment was influenced in part by the size of the dose as well as by the method of administration. Of greater significance, however, was the duration of symptoms. Those patients, whose

symptoms of polyneuritis were of several weeks or a few months' duration, showed a quicker response than those whose symptoms had lasted for one or more years. The average duration of time elapsed until improvement began was about 3 weeks for the entire series. Approximately 75% of the patients showed some improvement within 4 weeks.

TABLE 3.—RESULTS OF TREATMENT OF 520 CASES OF POLYNEURITIS WITH THIAMIN.

	Immediate results.		Late results remained well.		Had recurrence.	
	No.	%.	No.	%.	No.	%.
Unimproved . . .	15	3	0	0	0	0
Improved . . .	189	36	68	36	121	64
Symptom free . . .	316	61	122	39	194	61
Total . . .	520		190	37.5	315	62.5

The total duration of thiamin administration from the beginning until that time when no further increment of improvement was obtained, varied in response to the same factors. The average total duration of treatment was about 9 weeks for the entire series. Approximately 80% showed maximum improvement of relief of symptoms in 3 months or less.

TABLE 4.—ANALYSIS OF 62.5% OF RECURRENCES IN 505 CASES OF POLYNEURITIS IMPROVED ON THIAMIN ADMINISTRATION.

Length of observation after stopping thiamin.	Had one or more recurrences.		Remained well:		Total.
	No.	%.	No.	%.	
0 to 1 year . . .	37	21	139	79	176
1 to 2 years . . .	79	71	32	29	111
2 to 3 years . . .	81	85	14	15	95
More than 3 years . . .	118	96	5	4	123
Total . . .	315		190		505

A classification of this group based upon etiologic factors has been made.

The sum of the etiologic factors is in excess of the number of cases since, in some instances, at least two causative agents seemed to be concomitantly present. In the unknown group (indicated by question marks) no satisfactory etiologic explanation could be ascertained. This "X" group comprised 20% of all the etiologic factors and 22% of the actual number of cases.

A statistical survey was made of each different etiologic group to determine whether there was any difference in the type of response to thiamin. No significant change was noted. However, the unknown group seems to show a greater incidence of recurrence than that noted in other groups. In this 5-year study an insufficient time has elapsed to justify statistical evaluation of the frequency of recurrences in the different groups and therefore at this time no figures are presented in regard to this question.

The results of thiamin administration in this series of 520 patients is presented under two groupings. The first division is based upon an evaluation of the response to the first continuous course of thiamin administration: 3% were unimproved; 36% were improved and 61% became free of symptoms. After this first course was completed, thiamin was withheld and the patients were kept under observation for varying lengths of time. During these 5 years, 37.5% have remained either free of symptoms or as well as they were at the time that thiamin was discontinued; 62.5% have shown one or more recurrences of their symptoms in varying degrees of intensity. There was no significant difference in the per cent of recurrences in the improved group as compared to the symptom-free group.

A further statistical survey was made of the 62.5% of recurrences based upon the length of time that these patients were under observation since discontinuing the first course of thiamin treatment.

Of the entire series 35% were under observation less than 1 year since discontinuing thiamin. Of these, 176 patients (79%) maintained their improvement during that time and 21% had already begun to show return of symptoms.

The second group was under observation not less than 1 year and not more than 2 years. They represent 22% of the entire series. By this time the figures are almost reversed and now 71% have already had recurrence of symptoms and only 29% have maintained the beneficial effect of thiamin.

As a longer period of time passes, this trend of frequent recurrences becomes more apparent. In the third group (19% of the series) the percentage of cases with return of symptoms has risen to 85%.

The final group (24%) has been under observation for the longest period of time. Every patient has been observed for at least 3 years or more since thiamin has been withheld. By the time 3 or more years has elapsed, 96% of the cases have had one or more recurrences and only 4% have maintained their improvement or remained symptom free.

It becomes apparent from a study of this curve of recurrence that the beneficial effect of thiamin in cases of polyneuritis may be expected to continue for only a short period of time. Within about a year 50% of the patients have lost part or all of their relief; after 3 years over 90% have recurred; if the curve of the graph is extrapolated it may be assumed that at the end of 5 years, all or almost all of these individuals will have experienced a return of symptoms.

Many of these patients have received thiamin chloride for the treatment of their recurrent symptoms. A preliminary survey of the results of the treatment of the recurrences gives almost as encouraging results as for the initial response. About 90% of the recurrences respond by improvement or relief of symptoms to the readministration of thiamin chloride. Some of these patients have had 5 or more recurrences already and a few have been unable to remain free of symptoms unless they are constantly taking some

additional thiamin over and above the amount present in a well balanced diet.

In order to evaluate the results of the treatment of the recurrences a much longer period of time is needed. Thiamin in the pure form has been available only for about 5 years and this is too short a space of time in which to draw definite conclusions. It is hoped that at the expiration of 10 years a definite statement can be made in regard to the treatment of recurrences.

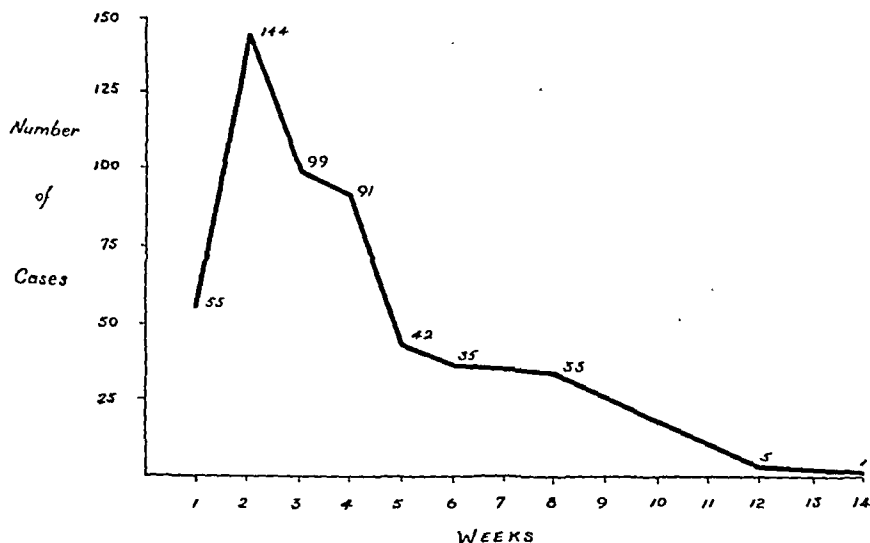


CHART 1.—Weeks of thiamin administration before beginning improvement.

Discussion. Polyneuritis is a clinical syndrome produced by many causes and the severity of the clinical manifestations seems to parallel the intensity of histo-pathologic changes in nerve tissue. Thiamin plays an important rôle in maintaining the normal balance of nerve tissue metabolism. The feeding of thiamin is followed by re-myelination and a return toward normal in the microscopic appearance of the nerve trunks.

Conceivably, in severe and advanced cases, irreversible changes may have taken place and the long continued use of large amounts of thiamin may be without effect. Based upon increasing clinical experience, it appears that, even in cases of 10 and 20 years' duration, the administration of thiamin is usually followed by some degree of improvement. Thus, in chronic polyneuritis, abatement of symptoms takes place even though after 3 or 4 years, the Achilles reflex and the vibratory sense have remained constantly impaired.

It has been demonstrated that the human requirement for thiamin is greater under a variety of conditions. Overwork, excess of carbohydrates in the diet, states of increased metabolism such as occur in hyperthyroidism, fevers and pregnancy, infections and perhaps even prolonged mental and emotional strain, all seem to increase the requirement for vitamin B₁ at times. This increased need seems

to vary in degree in different individuals and appears to exist in animals of many species as well as in human subjects.

Even when the amount of thiamin in the diet is adequate for health, changes in absorption and utilization of this vitamin within the body may bring about a state of relative avitaminosis. It is well known that the diet of many American families contains a minimum amount of thiamin necessary for health and in many such persons there may be little or no storage of this vitamin.

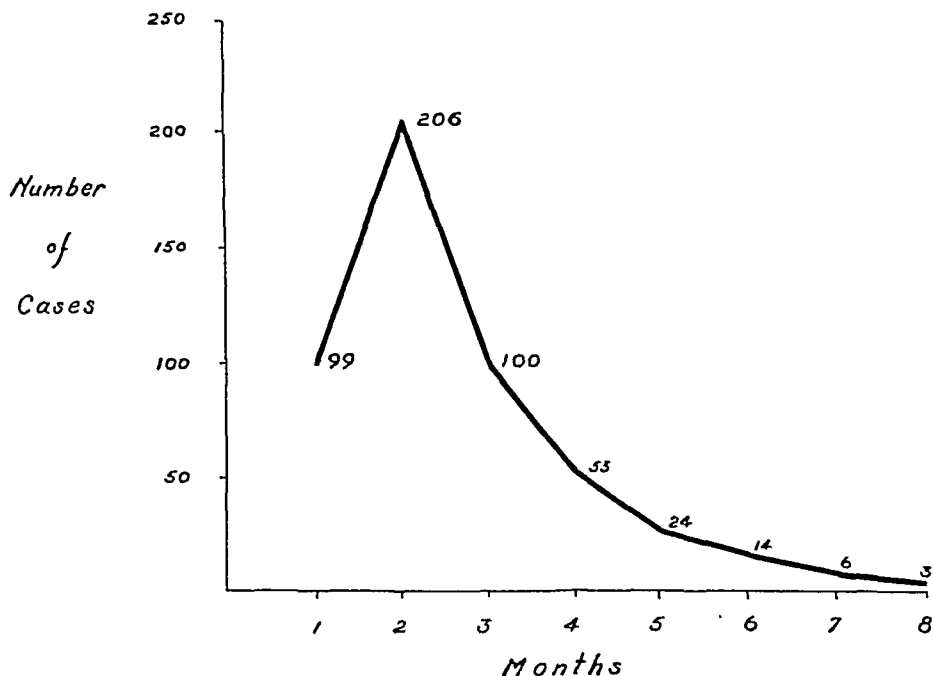


CHART 2.—Duration of first course of thiamin administration.

All these factors serve to explain the occurrence of polyneuritis in one individual during an infection or a pregnancy or after exposure to heavy metals; whereas other individuals, subjected to the same etiologic conditions, do not exhibit the clinical manifestations of polyneuritis. Furthermore, studies with animals have shown isolated instances in which one animal has an unexplained greater normal need for thiamin than other members of the same species. Human counterparts of such animals may exist and this theory may explain the fact that a few patients require a supplementary addition of thiamin to an adequate diet in order to maintain a satisfactory state of health.

This greater need for vitamin B₁ in some patients seems to be analogous to the greater need for iron in cases of primary hypochromic anemia. Here too is seen the same variation in the individual requirement for a normal food factor. Although the vast majority find enough iron in their daily food to maintain themselves in hemoglobin balance under normal conditions of life, there is a small number who require additional iron—and often in large

amounts—to keep their hemoglobin level up to normal. So too most individuals find enough thiamin in the normal diet to keep their nerve tissue metabolism in balance while a few seem to have an unexplained greater need for thiamin and are in better health when supplements of this vitamin—often in large amounts—are added to their food. It is hoped that future studies on larger numbers of normal and polyneuritic individuals will clarify this point and designate such cases by some such name as possibly cases of “Primary Hypothiaminosis.”

Summary. 1. A 5-year study of 520 cases of polyneuritis under thiamin chloride treatment is reported: 15 cases (3%) were unimproved; 189 cases (36%) were partially improved; 316 (61%) became symptom-free.

2. The 505 cases which were improved after taking thiamin chloride for an average of 9 weeks, were kept under observation after discontinuing this treatment. At the present time, 315 cases (62.5%) have had one or more recurrences of their symptoms.

3. Of 170 cases under observation up to 1 year after discontinuing thiamin, 21% showed recurrences. Of the 111 cases under observation from 1 to 2 years after discontinuing thiamin, 71% showed recurrences. Of the 95 cases under observation from 2 to 3 years after discontinuing thiamin 85% showed recurrences. Of 123 cases under observation more than 3 years after discontinuing thiamin, 96% showed recurrences.

Conclusion. The administration of adequate amounts of thiamin chloride to cases of polyneuritis is followed by a high incidence of improvement in symptoms. This effect usually begins to be apparent within 3 weeks and by 9 weeks reaches its maximum in most cases.

If thiamin is then discontinued, recurrence of symptoms takes place. At the end of 1 year about one-half of patients will have had one or more recurrences. At the end of 5 years all or almost all of the cases will have had some return of symptoms.

Readministration of thiamin in the treatment of these recurrences is highly effective.

It seems probable that some individuals have a greater normal need for thiamin than can be obtained from a normal diet. For such cases the term “Primary Hypothiaminosis” is suggested.

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BOOK REVIEWS AND NOTICES

HEADACHE AND HEAD PAINS. A Ready Reference Manual for Physicians. By WALTER FOREST DUTTON, M.D., Formerly Medical Director, Polyclinic and Medicochirurgical Hospitals, Graduate School of Medicine, University of Pennsylvania; Visiting Physician to Northwest Texas and St. Anthony's Hospitals; Director, Medical Research Laboratories, Amarillo, Texas. Pp. 301; 5 illustrations. Philadelphia: F. A. Davis Company, 1939. Price, \$4.50.

THIS book is presented as a ready source of reference in the management of headache. Following the introduction, which gives general principles of differential diagnosis and treatment, there follow thumb-nail sketches of various disorders from acromegaly to yellow fever. Useful prescriptions and procedures for the relief of headache are included. It should not supplant more complete sources of knowledge concerning the general medical aspects of diseases which have headache as a symptom. W. J.

RECENT ADVANCES IN MEDICINE. Clinical, Laboratory, Therapeutic. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School, etc., and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopaedic Hospital. Pp. 431; 42 illustrations. Ninth Edition. Philadelphia: P. Blakiston's Son & Co., 1939. Price, \$5.00.

A WELL-SELECTED list of advances in the field of clinical medicine, the subject matter being limited to methods used for medical patients in a general hospital. Both material and manner of presentation readily explain the popularity that has brought the work to its ninth edition.

R. K.

DIAGNOSIS AND MANAGEMENT OF DISEASES OF THE BILIARY TRACT. By R. FRANKLIN CARTER, B.S., M.D., F.A.C.S., Associate Clinical Professor of Surgery, New York Post-Graduate Medical School, Columbia University, New York City; Director of Surgery, Gouverneur Hospital; CARL H. GREENE, A.B., PH.D., M.D., F.A.C.P., Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University, New York City; Clinical Professor of Medicine, Long Island College of Medicine, etc.; and JOHN RUSSELL TWISS, A.B., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Assistant Physician, O.P.D., New York Hospital, New York City. Pp. 432; 84 illustrations and 6 plates. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

THIS book presents little that is new, but represents the considered opinions of a group of workers who for ten years have been operating a clinic for the study of the diseases of the biliary tract. It consists of a loosely arranged series of articles on various aspects of such diseases, especially those of the gall bladder. Not only the three named authors but eight others have contributed sections or chapters. Much of the literature up to 2 years ago

has been reviewed, as is indicated by approximately 30 pages of bibliography, and this constitutes one of its better features. Unfortunately no mention is made of the recent work on vitamin K and the bile salts in the control of the bleeding tendency in jaundiced patients. The discussions of diagnosis and treatment are confused and repetitious. The authors wisely insist in their introduction on a complete study of each patient, but their text and clinic charts have reference almost entirely to investigations of the biliary tract. The illustrations, however, are excellent and the book has a very satisfactory index which will make it useful for reference.

T. M.

YOU CAN'T EAT THAT! A Manual and Recipe Book for Those Who Suffer Either Acutely or Mildly (and perhaps unconsciously) from Food Allergy. By HELEN MORGAN. Foreword by DR. WALTER C. ALVAREZ of the Mayo Clinic. Pp. 330. New York: Harcourt, Brace & Co., 1939. Price, \$2.50.

AFTER 50 pages devoted to a foreword and chapters on the nature, causes, diagnosis and treatment of allergy (in which are dished up for lay consumption some dubious allergic doctrine and a lot of good practical information), the book really comes into its own when it gets out of the laboratory and into the kitchen. Part II offers a splendid selection of recipes covering a wide range of food avoidances and substitutes. Part III should be particularly welcomed by allergics because of its useful information about foods: "What's in it?" listing the ingredients in hundreds of brands of packaged goods; "Jokers in cooked foods," pointing out possible hidden contacts with common food substances; also lists of food substitutes and of sources of certain of the commoner foods and the various products that are made from them. An excellent book that both allergists and allergics will find helpful.

R. K.

RECIPES AND MENUS FOR ALLERGICS. By MYRA MAY HAAS. In Collaboration with NATHAN SCHAFER, M.D., Menus by CAY HILLEGAS. Illustrations by O. SOGLOW. Pp. 250; illustrated. New York: Dodd, Mead & Co., 1939. Price, \$2.50.

ALLERGISTS are keenly aware of the need for suitable dietary information for their patients and are grateful for every attempt made to fill this need. This volume offers an excellent selection of recipes and menus for those sensitive to egg, wheat and milk: 244 pages. Unfortunately that leaves only 6 pages for other food avoidances. This lack is partly met by an 18-page preface, discussing dietary problems and giving formulæ of many prepared foods and beverages as purchased in the open market.

R. K.

PRACTICE OF ALLERGY. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 1082; 338 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$11.50.

AN accurate, authoritative, well-written and complete presentation of our knowledge of allergy, and especially of its clinical aspects. Part I, introductory in nature, includes chapters on history, theories of anaphylaxis, comparisons of, and relations between, experimental anaphylaxis and clinical allergy; terminology. Part II (The General Characteristics of Clinical Allergy) discusses functional pathology, incidence of allergy; climate, environment, social status and heredity in allergy. Part III is on the Physiology of Allergy. Part IV, on Allergic Diagnosis, has chapters on discussion with the patient, skin testing, passive transfer, mucous membrane tests, patch test, leukopenic index, physical allergy, vital capacity, prepara-

tion of text extracts. Part V, on diagnosis and treatment of food allergy, includes chapters on food groups, the food diary, trial and elimination diets. Part VI gives extensive information on food allergens. Part VII takes up pollens, pollinosis and other inhalant allergy, including the available information on pollen surveys. Part VIII is on bacterial allergy, vaccines and focal infection. Parts IX to XV deal with fungi in allergy; entomogenous and diadermal (*e. g.*, serum sickness) allergy; anaphylactic shock; drug allergy, contact allergy, physical allergy and the use of drugs in the treatment of allergy. Part XVI, on the allergic diseases, has chapters devoted to asthma, hay fever and allergic rhinitis, migraine, skin diseases, gastrointestinal allergy, cardiovascular diseases, and miscellaneous diseases. This part, while adequate, has apparently been pruned a bit to keep down the size of the book. The author has brought to his task not only a thorough knowledge of his subject but also a facile pen and a clear and vivid mode of expression. The numerous illustrations are excellent and well-selected. The result is the best textbook on allergy. No allergist can afford to be without it, and practitioners and students will find it a valuable work of reference.

R. K.

THE MANAGEMENT OF TUBERCULOSIS IN GENERAL HOSPITALS. Patients, Staff, Employees. Prepared by WILLIAM H. OATWAY, JR., M.D., Assistant Professor of Medicine, University of Wisconsin Medical School; Assistant Physician, State of Wisconsin General Hospital for the Council on Professional Practice of the American Hospital Association. Pp. 78. Chicago: American Hospital Association, 1939. Price, Paper, 50 c. Cloth, \$1.00.

THE author states his reasons for believing that the care of a certain number of patients with active tuberculosis is a proper function of a general hospital. Methods of protection of contacts are discussed in minute detail. The striking incidence of active pulmonary tuberculosis in nursing and medical personnel is sufficient justification for this publication. It is especially recommended to the medical officer charged with the duty of defining and enforcing infectious precautions.

S. L.

TRAUMA AND INTERNAL DISEASE. A Basis for Medical and Legal Evaluation of the Etiology, Pathology, Clinical Processes, Following Injury. By FRANK W. SPICER, A.B., M.D., F.A.C.P. Pp. 593; 43 illustrations. Philadelphia: J. B. Lippincott Company, 1939. Price, \$7.00.

In his preface the author says: "The whole purpose of this book is to present a careful study of the role of trauma as an etiological factor in the causation of disease of the viscera and bodily structures, and a discussion of the etiology, pathology, clinical processes and end results of serious or apparently trivial injuries, together with their early or tardy manifestations and effects upon a healthy organ or structure and also upon organs or structures that present evidence of pre-existing disease." Major topics are the effects of trauma on the brain, the spinal cord, the chest and respiratory system; trauma and tuberculosis; trauma and the heart, the blood-vessels, the abdomen; trauma and gastric and duodenal ulcers; trauma of the liver and biliary system, the pancreas, the spleen; trauma and appendicitis; trauma and the genito-urinary system, the female genital tract; trauma and air embolism, diabetes, exophthalmic goiter, leukemia, syphilis; trauma and electrical injuries; trauma and tumors. There are quotations from over 1300 references in the literature. A profusion of illustrative case reports makes the presentation vivid and convincing. Each section ends with a brief and convenient summary. The author brings to his task an experience

of 30 years as a surgeon. He has ably marshalled his facts, has presented both sides of the argument in controversial matters, and has drawn his conclusions in a logical and conservative manner. The result is a book of the first importance, that fills a real need in medical literature. It should prove valuable to surgeons, especially from the standpoint of diagnosis; to internists, especially because of the valuable information on the late medical results of trauma, and to all physicians because of the obvious medico-legal implications.

R. K.

ELEKTRODIAGNOSTIK. By DR. B. NEOUSSIKINE and DR. D. ABRAMOWITSCH, Tel Aviv. Pp. 242; 30 illustrations. Bern: Hans Huber, 1939. Price, Schw. Fr. 12.

ELECTRODIAGNOSIS has lost some credit during the last decades. We have come to understand that percutaneous measurement of intensity and voltage of currents though a numerical method is too crude a procedure to be of help for finer diagnosis while qualitative changes in muscular contraction can be judged only by subjective observation. The more recent methods of examining the irritability including the time factor, on the other hand, have not yet been generally accepted because it is unjustly believed that their application is difficult. The aim of the authors of this book is "to adapt the experimental results in the field of general physiology of irritability to the practical purpose of clinical electrodiagnosis." This plan has been successfully accomplished. In the first chapter of this book the physical and physiologic data underlying the methods of electrical examination of the nerve muscle apparatus are explained in clear, simple language. The next chapter deals with qualitative and quantitative changes of irritability, with the methods of galvanic and faradic excitation, with chronaximetry and the technique of the various methods. The following 2 chapters discuss the results of the electrical examination in relation to general physiologic problems and to the pathology of the motor nervous system in nervous and muscular diseases. Finally, methods and results of electrical examination of the sensory system, the sense organs and the vegetative nervous system are described. A bibliography would greatly increase the value of the book. Those who want to familiarize themselves more intimately with the subject will regret that the authors have confined their discussion to the classical chronaxie, omitting the importance of determining strength, duration and lambda curves as well as the application of tubes in modern instruments. The book shows throughout the personal experience of the authors. It is not a "technical" book, but is written for the general practitioner and the clinical neurologist.

F. L.

NEW BOOKS.

The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 12, Tetanus to Yellow Fever. Under the General Editorship of Sir HUMPHRY ROLLESTON, Br. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 726; 48 illustrations, and 12 plates (3 in color). London: Butterworth & Co. (Publishers), Ltd., 1939. Price, \$12.00.

Office Gynecology. By J. P. GREENHILL, B.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago; Professor of Gynecology, Cook County Graduate School of Medicine, etc. Pp. 406; 104 illustrations. Chicago: The Year Book Publishers, Inc., 1939. Price, \$3.00.

Die Arbeitstherapie der Zuckerkranken. By PROF. DR. GERHARDT KATSCH, Direktor der Medizinischen Universitätsklinik in Greifswald und des Deutschen Diabetikerheimes in Gerzauf Rügen. (Sonderausgabe aus "Ergebnisse der physikalisch-diätetischen Therapie," Band 1.) Pp. 35; 3 illustrations. Dresden: Theodor Steinkopff, 1939. Price, Rm. 2.50.

Teaching Wholesome Living in the Elementary School. By ALMA A. DOBBS, M.A., Curriculum Division, Los Angeles City Schools, Los Angeles, Calif. Pp. 304; illustrated. New York: A. S. Barnes & Co., Ltd., 1939. Price, \$2.50.

Die Biologische Reaktion. Eine Funktionelle Analyse und Synthese Biometrischer Werte zur Zahlenmässigen Erfassung von: Allergie, Allgemeiner Resistenz, Spezifischer Resistenz, Krankheitsintensität, Extensität Aktiver Herde Immunität. Pp. 263; 335 illustrations. Bern: Hans Huber, 1939. Price, Schw. Fr. 42.80.

"This is based on the fundamental premise that children should be encouraged and be taught to grow in all ways . . ." socially as well as intellectually.

The Neurogenic Bladder. By FREDERICK C. McLELLAN, M.S., M.D., Instructor in Surgery, University of Michigan Medical School, Ann Arbor. Pp. 206; 9 illustrations and 49 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, \$4.00.

Psychobiology and Psychiatry. A Textbook of Normal and Abnormal Behavior. By WENDELL MUNCIE, M.D., Associate Professor of Psychiatry, Johns Hopkins University; Assistant Psychiatrist, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital. With a Foreword by ADOLF MEYER, M.D., LL.D., Sc.D., Henry Phipps Professor of Psychiatry and Director of the Department of Psychiatry, Johns Hopkins University. Pp. 739; 69 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$8.00.

Injuries of the Nervous System Including Poisonings. By OTTO MARBURG, M.D., Clinical Professor of Neurology, Columbia University; Research Neuropathologist, Montefiore Hospital, New York, etc., and MAX HELFAND, M.D., Assistant Clinical Professor of Neurology and Psychiatry, Columbia University; Chief of Nerve Clinic, Post-Graduate Hospital, New York, etc. Pp. 213; 16 illustrations. New York: Veritas Press, 1939. Price, \$3.00.

The Medical Clinics of North America, Vol. 23, No. 5 (Boston Number, September, 1939). Pp. 302; illustrated. Philadelphia: W. B. Saunders Company, 1939.

A timely symposium of 8 papers on sulphanilamide precedes 13 papers, mostly on diagnosis and treatment, on such diverse topics as diagnostic procedures in allergic diseases and human and social problems in caring for patients.

A *History of Tropical Medicine.* Based on the Fitzpatrick Lectures delivered before the Royal College of Physicians of London 1937-1938. In Two Volumes. By H. HAROLD SCOTT, C.M.G., M.D., F.R.C.P., Lond., D.P.H., D.T.M., and H. CAMB, F.R.S.E., Director, Bureau of Hygiene and Tropical Diseases; Member of the Colonial Advisory Medical Committee, etc. Pp. 1165; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, \$12.50 per set.

Die Funktion der Nebennierenrinde. By F. VERZAR, Professor der Physiologie an der Universität Basel. Pp. 266; 16 illustrations and 4 tables. Basel: Benno Schwabe & Co., 1939. Price, Fr. Sw. 25.00.

Tumors of the Skin. Benign and Malignant. By JOSEPH JORDAN ELLER, M.D., Attending Dermatologist, City Hospital, New York City; Consulting Dermatologist, French and Broad Street Hospitals, New York, etc. Pp. 607; 403 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$10.00.

Treatment of Some Common Diseases (Medical and Surgical). By Various Authors. Edited by T. ROWLAND HILL, M.D. (LOND.), M.R.C.P. (LOND.), Physician to the Southend General Hospital; Assistant Physician to the West End Hospital for Diseases of the Nervous System, etc. Pp. 398; 90 illustrations (several in color) and many x-rays. Baltimore: The Williams & Wilkins Company, 1939. Price, \$5.00.

Circulatory Diseases of the Extremities. By JOHN HOMANS, M.D., Clinical Professor of Surgery, Harvard Medical School. Pp. 330; 29 text illustrations and 13 plates. New York: The Macmillan Company, 1939. Price, \$4.50.

Psycho-Dynamics of Chewing. By H. L. HOLLINGWORTH, Columbia University. (Reprinted from Archives of Psychology, No. 239, R. S. Woodworth, Editor.) Pp. 89. New York: Archives of Psychology, 1939. Price, \$1.50.

Cæsarean Section. Lower Segment Operation. By C. McINTOSH MARSHALL, F.R.C.S. (ENG.), Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. Pp. 230; 107 illustrations and 2 colored plates. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.50.

Ophthalmology. By BURTON CHANCE, M.D. Vol. XX of Clio Medica. A Series of Primers on the History of Medicine. Pp. 240; 6 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.00.

Clinique et Pathologie Comparee, Vénérologie—Cancérologie—Dermatoses—Médecine Générale—Phyto-Pathologie. By LOUIS BORY, Chef de Clinique de la Faculté de Médecine de Paris à l'Hôpital, Saint Louis, Prix Duchenne de Boulogne, 1937. Pp. 239. Paris: Masson et Cie, 1939. Price (paper), Fr. 50.

NEW EDITIONS.

Practical Obstetrics. By P. BROOKE BLAND, M.D., Emeritus Professor of Obstetrics, Jefferson Medical College; Consulting Obstetrician, Jefferson Medical College Hospital, Philadelphia, and THADDEUS L. MONTGOMERY, M.D., Clinical Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 877; 502 illustrations, including 27 colored plates. Third Revised Edition. Philadelphia: F. A. Davis Company, 1939. Price, \$8.00.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1144; 218 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$9.50.

The popularity of this excellent work is demonstrated by the use that our shelf copy received, as well as by the appearance of a new edition within 2 years. "An idea of the extent of the revision can be gained from the following information: Over 1400 new references have been added, those to original articles appearing as footnotes, those to general reviews being grouped at the ends of chapters and reference to them is made parenthetically in the text. It may be reemphasized that the purpose of such references is not to assign priority or to allot credit, but rather to furnish 'leads' to a more extensive bibliography. Whenever possible, the more recent references are given preference. The illustrations have been increased in number and many older ones replaced by new and better ones. Altogether 52 new illustrations have been added. It is estimated that over one-third of the text has been completely rewritten, and the other parts have undergone numerous and significant changes."

Infections of the Hand. By LIONEL R. FIFIELD, F.R.C.S. ENG., Late Surgical Registrar and First Assistant and Demonstrator of Anatomy, London Hospital, etc. Pp. 167; 57 illustrations, including 8 plates (2 colored). Second Edition by PATRICK CLARKSON, F.R.C.S. ENG., Surgical Tutor, Guy's Hospital; Demonstrator of Anatomy and of Operative Surgery, Guy's Hospital Medical School. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.25.

Blood Groups and Blood Transfusion. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City. Pp. 306; 52 illustrations and 86 tables. Second Edition. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.00.

Synopsis of Pediatrics. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals, assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine and Assistant Pediatrician to the St. Mary's Group of Hospitals. Pp. 430; 144 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1939. Price \$4.00.

Textbook of Nervous Diseases. By ROBERT BING, Professor of Neurology, University of Basel, Switzerland. Translated and enlarged by WEBB HAYMAKER, Assistant Clinical Professor of Neurology and Lecturer in Neuro-Anatomy, University of California. Pp. 838; 207 illustrations (9 in color). From the Fifth German Edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$10.00.

This translation of the 5th revised edition of Bing's *Lehrbuch der Nervenkrankheiten*, having undergone some rearrangement and augmentation, is now better adapted to American and English usage. Emphasis is given to precise and detailed therapeutics. Thoroughly abreast of all that is new and important, its popularity will doubtless continue.

Obstetrical Practice. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 858; 1043 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$7.00.

Physiological Chemistry. A Text-book for Students. By ALBERT P. MATHEWS, PH.D., Andrew Carnegie Professor of Biochemistry, The University of Cincinnati. Pp. 1488; 113 illustrations. Sixth Edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$8.00.

Stedman's Practical Medical Dictionary of words in medicine with their derivation and pronunciation including dental, veterinary, chemical, botanical, electrical, life insurance and other special terms; anatomical tables of titles in general use, the terms sanctioned by the Basle Anatomical Convention; the New British Anatomical Nomenclature; pharmaceutical preparations official in the U. S. and British Pharmacopœias or contained in the National Formulary; and comprehensive lists of synonyms. By THOMAS LATHROP STEDMAN, A.M., M.D., Editor of the Twentieth Century Practice of Medicine; of the Reference Handbook of the Medical Sciences, etc., and STANLEY THOMAS GARBER, B.S., M.D. Pp. 1303; illustrated. Fourteenth Revised Edition with Etymologic and Orthographic Rules. Baltimore: The Williams & Wilkins Company, 1939. Price, \$7.50 with Thumb Index, \$7.00 without Index.

Shortly before Dr. Stedman's death in 1938 he persuaded his nephew to collaborate with him in the revision of this edition, the continuance of which it is hoped will be thus assured. It contains the usual number of new words necessitated by medical progress, especially in the fields of hormones, vitamins, and new chemical compounds. It is to be hoped that in this excellent dictionary Stedman's influence on the improvement of medical orthography will be continued.

PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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URGENT SURGERY.

No more important exigencies exist in medicine than an unusually severe hemorrhage from the nose or throat, or an acute laryngeal obstruction. Such occurrences, often tempered by an onset that is both sudden and dramatic, call for cool judgment and occasionally for unparalleled rapidity of action in order to correct the urgent and pressing need for relief. Here the indications for therapeutic action are unequivocal, uncompromising and insistent. There is, on the other hand, an entire group of oto-rhino-laryngologic events which possesses one saving grace, that of permitting the surgeon a limited period of time for adequate study, diagnosis and for the decision to intervene surgically at an optimum time interlude. These relative urgencies—intubation, foreign bodies in the tracheobronchial tree and in the esophagus, occasionally tracheotomy, carotid and jugular ligation, retropharyngeal abscess, mastoiditis, osteomyelitis and meningitis, to name an important few—do not countenance deliberate procrastination. For to procrastinate is to invite possible disaster; to act courageously is to succeed in cases which otherwise might appear hopeless. Although urgent surgery has commanded the attention of surgeons everywhere for centuries, it is unfortunate that the Quarterly Cumulative Index Medicus fails to list those numerous cases which so appropriately fall under the heading "Urgent Surgery."

While fatal hemorrhage from the throat occurs comparatively infrequently, still it does occur too frequently. Many patients die from hemorrhages that are unannounced, sudden and overwhelming—but avoidable. Free active hemorrhage from the throat, with or without apparent inflammation, requires not local treatment but bold external operative measures. Thus, in their thoughtful analysis of 6 cases of pharyngomaxillary infection, White and Hubert²⁶ assert that if any doubt exists regarding erosion of the internal carotid artery, the external carotid and the ascending pharyngeal arteries should be ligated and a loose ligature placed around the common carotid artery. Ligation of the common carotid artery, when it is done slowly (in minutes, not seconds)

and with an attempt actually to prevent the flow of blood beyond the ligatures, is a life-saving procedure, as compared to temporizing methods of operation by the intrapharyngeal route. That spontaneous hemorrhage into the maxillary sinus occurs as a complication of hyperplastic maxillary sinusitis is revealed by Hall and Thomas.⁹ No underlying general systemic or vascular disease was found concurrent or coëxistent with the hemorrhage taking place in a series of 12 patients. Although an external radical operation on the antrum was performed with successful results in 10 of the 12 patients, they are now convinced that if the literature had been sufficiently clear they could have avoided radical surgical intervention in all but one of the cases. In this case the hemorrhage was so severe that the patient's hemoglobin was down to 58%. It is in this type of case that an operation, which has as its purpose control of the hemorrhage and complete inspection of the endoantrum, is a rational procedure. In a brief discussion of the emergencies in ear, nose and throat, Kully¹² rapidly reviews the therapeutic measures employed in nasal hemorrhage, the control of postoperative tonsil and adenoid hemorrhage, the fractured nose and acute laryngeal obstruction.

An acute laryngotracheobronchitis occurring in an eleven-month-old infant girl is described by Cassidy.⁴ Relief following tracheotomy was transient, in spite of continued use of the oxygen tent. Efforts to improve aëration by means of aspiration of the trachea through the tracheotomy tube gave only temporary relief. Eventually, repeated bronchoscopic inspection through the tracheotomy wound to relieve cyanosis and dyspnea assumed a prominent part in maintaining life. Bronchoscopic aspiration was deferred each time as long as possible and resorted to only when the patient's condition was alarming and the clearing of the airway was imperative. A total of 38 aspirations—each procedure commandingly urgent—was done over a period of 13 days before dyspnea ceased. Acute laryngeal stenosis in children with urgent laryngeal dyspnea requires intubation or tracheotomy for immediate relief. Patterson¹⁶ believes that there are no contraindications to tracheotomy for obstructive laryngeal dyspnea. When properly performed, complications are rare and stenosis of the larynx does not result directly. Although in most cases stenosis is the result of faulty tracheotomy, it is paradoxical that the first step in its correction of a stricture is a repetition of the tracheotomy procedure. Weinstein²⁴ reports 3 cases, each of which presented the symptom of obstructive laryngeal dyspnea, but in each of which the fundamental etiology was different; namely, hypopharyngeal foreign body in an infant, with occlusion of the laryngeal lumen; streptococcic laryngotracheitis in a child with edema of the larynx; and edema of the larynx, complicating agranulocytic angina following sulphanilamide therapy. The first case died before a tracheotomy could be done, the second had a successful termination following tracheotomy, and the third died on the table in spite of a tracheotomy. In the treatment for stenosis in bilateral abductor paralysis of the larynx, Rawlins¹⁸ presents a successful unilateral operation. Certain modifications of the principles suggested by Loré's anatomic study were used. The operated cord was moved not only to an external position, but was also maintained on a definitely lower level than the operated side. In analyzing 127 cases of laryngotracheobronchitis Richards¹⁹ found that there were 37 deaths. In the tracheot-

omized cases the mortality was 51%. Despite the high mortality, tracheotomy is considered the method of choice, for if the condition is permitted to go on until it is an obstructive emergency or the patients are toxic and exhausted, hope of recovery is slight.

The causes of esophageal rupture are enumerated by Hunt¹¹ as being due to foreign bodies, faulty instrumentation and malignant tumors. He analyzes 20 cases of upper mediastinal involvement following perforation. The diagnosis of cervical periesophageal abscess was confirmed in each case by roentgenogram. Sixteen of the 20 cases were operated on and external drainage established, with 12 recoveries and 4 deaths. Four cases were treated conservatively. The unoperated cases died. He claims that early drainage of the infected area is definitely indicated. The mortality is low if drainage is thoroughly established while the infection is localized in the region of the perforation. Untreated cases are fatal if a real abscess has developed. External operation and drainage is more thorough and effective than intra-esophageal drainage. Procrastination in operating means disaster, boldness means recovery. Butler³ and his associates emphasize the need for educating the medical profession and the laity regarding the dangers due to aspirated foreign bodies. Prompt diagnosis and prompt removal of foreign bodies are of the utmost importance. Prolonged residence, without bronchial obstruction or trauma to lung parenchyma, may be well tolerated; but prolonged residence with bronchial obstruction is tolerated poorly and leads first to acute suppurative pneumonitis, and later, if the patient survives, to chronic bronchiectasis. Acute suppurative pneumonitis carries a high mortality and bronchoscopic efforts are not well tolerated. Bronchiectasis is incurable save by radical surgery.

Pus deep in the neck calls for the surgeon's best judgment, skill and courage. Delay in early and courageous treatment of deep infections of the neck may prove dangerous. Orton¹⁵ and Pearse¹⁷ emphasize the hazards of treating all cervical infections conservatively until fluctuation occurs, for in some cases surgery at an early stage is necessary to save life. However, it is just as dangerous to operate prematurely on a localizing infection as to withhold operation after involvement of a fascial space. Grodinsky⁸ concludes from an anatomic and clinical study of retropharyngeal and lateral pharyngeal abscess that the treatment of these serious conditions is chiefly surgical—that is early and adequate drainage. Four cases of Ludwig's angina, all of which were cured by operative intervention, are described by Fabricant.⁶ He believes that only early diagnosis and prompt operation can save the life of the patient with Ludwig's angina. A transverse incision is employed in the infiltrated area for wide exposure of the involved tissues. When necessary, the incision may extend around the entire circumference of the mandible; thus injury to the facial artery and veins is avoided. The infiltrated muscles are cut transversely and the sublingual space widely opened up. Wessely²⁵ maintains that inflammatory diseases of the cellular tissue spaces of the neck are particularly dangerous because the anatomy of this region favors direct propagation of the infection to the mediastinum, middle cerebral fossa and the circulation. Since endocranial infection can be helped only in the beginning, imme-

diate surgical intervention is indicated in infection of the parapharyngeal space as soon as the diagnosis is made.

Due to the popularity of automobiles, aeroplanes and other rapidly moving conveyances, accidents to the head and neck have increased proportionately. Injuries to the larynx have become more common. Lacerations are often deep, with resulting deformity and stenosis. Looper¹⁴ proposes an operative procedure in which the hyoid bone is utilized as a graft in the treatment of laryngeal stenosis in selected cases. The principle depends on embedding the left end of the attached hyoid bone between the incised thyroid cartilage, to act as a wedge in enlarging contractures and deformities of the larynx and to permit a better airway. The term "compound injuries of the face" is applied by Brown² to designate any serious facial injury to soft tissues or bone. Automobile injuries are often of this type and are frequently as bizarre as those of firearm injuries. There may be cranial and cervical-spine injuries complicating the facial injury. It is best to care for these wounds and fractures in the first 12 to 24 hours, before swelling, organization of the clots, and infection have occurred. If seen later, manipulation of the parts can be delayed, but the soft parts may still be approximated. In a symposium on head trauma Whitham²⁷ states that fractures of the bones of the face are more frequent than ever before. Unless the patient is in a dying condition, an immediate attempt should be made to correct the bony deformity in most cases. Wounds of the frontal bone should be carefully explored for depressed fractures, such depressions relieved and the cases treated on general surgical principles. Fractures of the upper jaw are nearly always associated with fractures of other bones of the face, and conversely, fractures of the bones of the face are nearly always associated with fractures of the upper jaw. Gerrie⁷ reflects upon his experiences with 100 cases of nasal fractures and discusses such matters as anesthesia, the technique of reduction, internal splinting and external splinting. He feels that repositioning of the fragments in a nasal fracture becomes increasingly difficult and less certain as time elapses, and so, regardless of swelling or laceration, is done as soon after the injury as is expedient.

After studying 15 cases of proved thrombophlebitis of the sigmoid sinus and jugular bulb, Druss⁵ advances the opinion that the basic principle implied in the surgical treatment of sinus thrombosis (*i. e.*, eradicating the focus in the bone and in the sigmoid sinus and attempting to seal off the infection from the blood stream by ligation of the jugular vein and by obliteration of the sinus beyond the apparent site of disease in the vein) is still fundamentally sound. At times he feels that it is advisable to modify or omit one or all of the steps. Smith²¹ writes that bilateral thrombophlebitis of the lateral sinuses complicating bilateral acute mastoiditis occurs more frequently than one would judge from the literature. Patients with this condition usually present a desperate picture, and there is no doubt, judging from the recoveries reported, that many of them may be saved if the sinuses are blocked and the veins tied, and that if this is not done the condition is likely to terminate fatally. The necessity for early recognition of meningeal irritation, the institution of prompt surgical intervention for the removal of the focus and the value of sulphanilamide are advocated by Bowers¹

in describing the operative treatment of otitic meningitis. Hirst¹⁰ reports 2 cases of osteomyelitis of the skull complicating mastoiditis and frontal sinusitis. In analyzing the records of published cases, he finds that this tragic sequel to mastoiditis or frontal sinusitis has occurred in cases in which there was no surgical intervention and in others in which it was thought that there was too little or too much surgical intervention. In general, he believes that once diagnosis has been established, radical operation with wide resection of bone should be done for a cure.

Maintaining that acute osteomyelitis of the superior maxilla in children requires early operative intervention, Lacy and Engel¹³ state that drainage should be established primarily through the mouth and secondarily through the antrum of Highmore. Maxillary sinusitis is a complication of the osteomyelitis rather than a cause of it. The prognosis is not bad when there is early surgical intervention. In an excellent review of the reported cases of meningitis from the sphenoid sinus, Teed²³ concludes that while the sphenoid sinus is involved in about 15 % of clinical cases of sinusitis and in 33 % of pathologic cases, it is nevertheless responsible for approximately 35 % of all rhinogenous intracranial complications. He expresses the hope that the future management of these cases of serious involvement will be more radical and successful. Malignant melanoma must be considered in cases in which papilloma occurs in the anterior part of the nasal cavity, springing either from the turbinates or from the floor of the nose. Smith²⁰ describes his experiences with 2 cases of primary melanoma of the nasal cavity. In both cases the growth of the primary lesion was slow compared to the rapid dissemination of the metastatic tumors. This indicates that a more complete removal of the tumor, with a wide margin of normal tissue, would offer an excellent chance of cure. Wide exposure and removal by means of an external approach should be carried out as soon as the diagnosis has been confirmed by careful histologic study. In surveying the optic nerve complications of accessory nasal sinus disease, Strauss and Needles²² state that although they are mindful of the frequency of multiple sclerosis as a cause of retrobulbar neuritis, of the large percentage of these cases that spontaneously recover with or without conservative nasal treatment, and mindful of the fact that diseased sinuses may erroneously be incriminated as the cause of a host of conditions, they nevertheless believe that in some cases operative intervention is indicated. If the rhinologist concludes that the sinuses are diseased, and no other cause for the neuritis is present, the authors, as neurologists, favor eradication of the focus. Especially if continued observation shows progression in the visual impairment.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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CHEMICAL TRANSMISSION OF NERVOUS IMPULSES.

APPLICATION of the principles of chemical transmission of nervous impulses to the elucidation of the pathologic physiology of myasthenia gravis and myotonia congenita, with the resulting better understanding of the action of therapeutic agents in these diseases, has directed the attention of clinical neurologists toward the evidence on which this theory of nervous activity rests.

The mode of transmission of the nervous impulse across the synapse, and from the nerve ending to the effector organ, has always been difficult to explain on the basis of a physical, or electrical concept. The lack of continuity of the tissues involved, and the unidirectional character of the flow, have not been easily fitted into any such theory so far evolved. Thus a stimulus was provided for a search for some other mode of transmission more in keeping with known physiologic laws.

After the discovery of the remarkable activity of extracts of the suprarenal gland by Schafer in 1894, with the subsequent isolation of epinephrine as the active constituent, it was soon apparent that this substance on injection showed effects closely parallel to those produced by sympathetic stimulation. These effects were antagonized in both cases by ergotoxine. That the effect of epinephrine is on the effector cells, and not on the nerves, is shown by the fact that it persists after degeneration of all nervous elements. More recently, Cannon and his co-workers have shown that this substance is produced on stimulation of sympathetic nerves at their endings, and although they are not ready to state that the substance produced on stimulation is actually epinephrine, and prefer to call it "sympathin," there can be no doubt that a very close relationship prevails. Thus we have a well-established chemical mediator of postganglionic sympathetic impulses, the existence of which is conceded by all.

Roughly paralleling the growth of knowledge of this mediator of sympathetic impulses, more and more was being learned about a sub-

stance that reproduced parasympathetic stimulation. In 1914 Dale³ isolated from ergot a compound which he found to possess two distinct and important actions. First, he demonstrated an action similar to that of muscarine; that is, effects paralleling those of parasympathetic stimulation, and of fleeting duration, antagonized by atropine. Second, and distinct from the parasympathetic action, he found the substance to stimulate voluntary muscle and all autonomic ganglia; in other words, an action similar to that of nicotine. Important as these discoveries were from the pharmacologic aspect, the fact that the substance was not elaborated by any of the glands of internal secretion, as was the case with epinephrine, or even at that time demonstrated in the animal body, prevented its rôle in nervous transmission from being so readily appreciated.

First definite proof of chemical mediation of both sympathetic and parasympathetic impulses was the result of simple but fundamental experiments reported by Loewi.¹⁰ The vagus nerve to the heart of the frog contains both parasympathetic fibers which slow the heart, and sympathetic fibers which cause its acceleration. Which of these effects will predominate at any time depends on the functional state of the preparation and the season. Loewi found that if he placed the effluent from one isolated heart after vagus stimulation into a similar preparation which had not been stimulated, the second unstimulated preparation behaved identically as had the stimulated one, whether this had consisted of acceleration or slowing. Moreover, he found that if the first preparation were treated with atropine or ergotoxine, the slowing or acceleration was not manifest, but that these actions did become apparent when the effluent was transferred to the second preparation not so treated. The most important part of his contribution was, however, that he identified the substance causing the slowing as a labile choline ester, which he showed to have all the properties of acetylcholine as described by Dale 7 years before. Further than this, he demonstrated that the fleeting action of the substance was due to its rapid splitting by an esterase, and that the long recognized action of physostigmine in prolonging and intensifying parasympathetic action was due to its ability to render this esterase inactive, and thus delay the breakdown of the acetylcholine. Thus a tool was provided whereby the extremely labile mediator could be preserved for experimental identification. Much of the subsequent work has been made possible by this maneuver, with the use of leech muscle as a very sensitive indicator of the presence of the acetylcholine. Subsequently, it has been shown by Stedman and Stedman¹⁶ that this esterase is highly specific for choline esters, and that not only physostigmine but other chemically related compounds are capable of inactivating it, presumably by combining with its reactive groups.

As yet, this intriguing agent had not been demonstrated in the animal body, a definitely weak link in the chain of circumstances favoring its consideration as a chemical mediator. It remained for Dale to isolate it in relatively large amounts from the spleen of the horse. When this was followed by its recovery in crystalline form from the brain by Stedman and Stedman, its presence in nervous tissue, if not its rôle in nervous transmission, was definitely established.

Thus was fairly definitely established the chemical nature of transmission of nervous impulses at the autonomic nerve endings, with

epinephrine or "sympathin" and acetylcholine as the chemical mediators. Interest was renewed in the somewhat arbitrary division of the autonomic system into sympathetic and parasympathetic, and Dale put forward the very useful concept of a more rational division of autonomic nerve fibers into "cholinergic," being those which on stimulation gave a response characteristic of that to acetylcholine, and "adrenergic," those which gave an epinephrine-like response. The effects of the former are antagonized by atropine, of the latter, by ergotoxine. There are some rather striking differences between this and the anatomic classification. Thus the sweat glands, with innervation from the sympathetic, are cholinergic rather than adrenergic.

The characteristics of the time relationships of formation and destruction of both proposed chemical mediators are quite in keeping with the rather slow onset and relatively persistent action associated with autonomic activity, especially in the periphery. We must remember, however, that Dale found, besides its muscarine-like activity, which accounted nicely for the parasympathetic activity, that acetylcholine had a nicotine-like activity, stimulating ganglion cells and voluntary muscle fibers. Thus it is not too surprising to find stimulation of the perfused cervical sympathetic ganglion of the cat, when treated with physostigmine, showing the presence of acetylcholine in the effluent. This is, indeed, precisely what was found by Feldberg and Gaddum.⁵ Although this finding has been controverted by Lorente de No,¹¹ who stated that the acetylcholine appeared only as a result of injury, and also was present without stimulation, thus falling in the category of a general metabolite rather than a chemical mediator, the recent careful work of MacIntosh¹² seems to show fairly conclusively that if any artefact existed, it was in Lorente de No's experimental procedure rather than in the original work. Moreover, it has been shown by Feldberg and Vartiainen⁷ that the elaboration of acetylcholine occurs only on stimulation of the preganglionic fibers to the ganglion, accounting for unidirectional conduction at the synapse.

While acetylcholine is very labile, choline esterase is quite stable, persisting undiminished for 48 hours after death of tissues. Since this enzyme is so specific for choline esters, it would seem reasonable to suppose that it would be concentrated in the body where it might have a useful function to perform, that is, where nerve impulses would be forming acetylcholine. Thus it is a reasonable assumption that the amount of choline esterase present is a fair indication of the production of acetylcholine. That this is indeed so has been shown by Nachmansohn,^{15a-d} who has demonstrated very nicely that the amount of choline esterase present in tissue is directly related to the number of synapses or terminal nerve fibers present. He has also shown that the amount of esterase in an autonomic ganglion is adequate to split the amount of acetylcholine that would be expected to be formed as the result of stimulation, in a period corresponding to the refractory period of the preparation. Thus chemical transmission across synapses in the ganglia can be adequately explained with acetylcholine as the mediator.

It remained for Brown and his co-workers^{1,2,4} to show that the other nicotine-like action of acetylcholine, stimulation of voluntary nerve fibers, is also utilized in the animal body. Ordinary application of acetylcholine to a mammalian muscle preparation is effective in causing a slow contracture, but no rapid twitch such as is characteristic of a

single nervous volley. However, if the acetylcholine is injected intra-arterially into a muscle devoid of blood, and so effects a fairly high immediate concentration therein, such a twitch is seen. This is readily understandable, as in the physiologic state, a nerve impulse might be expected to effect a high concentration of acetylcholine in a very small area, that is at the motor end plate, while the concentration of acetylcholine in the muscle as a whole would be very small, because of the relatively minute amount of muscle bulk occupied by the end plates. In accord with this, Nachmansohn¹⁴ has found in the frog sartorius, where all the end plates are concentrated in a small portion of the muscle, a high concentration of choline esterase in that portion with very little elsewhere in the muscle. He has also shown that here again the amount of esterase present is adequate to accomplish splitting of the acetylcholine in the very short refractory period of the muscle. Thus the preponderance of evidence is at least compatible with the acceptance of acetylcholine as the chemical transmitter of nerve impulses from the motor nerve to the voluntary muscle fiber.

Whether acetylcholine will be found to be important in the transmission of nerve impulses across synapses in the central nervous system remains to be seen. The evidence available at present, although favorable to such a concept, is as yet too fragmentary to be more than suggestive. Stedman and Stedman have isolated acetylcholine from brain tissue, while Nachmansohn has shown the concentration of choline esterase in various parts of the brain to be proportional to the number of synaptic connections present. It has also been demonstrated that there is in the cortex an enzymic system capable of synthesizing acetylcholine aëroically.¹³ Nor is the mode of transmission even where acetylcholine is generally conceded to be the mediator entirely clear. Just how the liberation of the effective concentration of acetylcholine is achieved is not evident. Two possibilities suggest themselves: synthesis of the compound, or its liberation from an inactive state. Both have their supporters, but evidence is scanty. It is, however, known that in the passage of an impulse along a nerve fiber there is an accumulation of potassium ions on the surface of the axone, and it has been demonstrated that the addition of potassium in the ganglion causes a liberation of acetylcholine.⁶

The practical application of the rôle of acetylcholine in transmission of nerve impulses from motor nerve endings to voluntary muscle fibers has been in relation to the two conditions, myasthenia and myotonia.^{8,9} These conditions present diametrically opposed pictures. In myasthenia, there is a defect in muscular contraction, with easy fatigability, while in myotonia there is a defect in relaxation. It is well known that in myasthenia the administration of physostigmine, and even more so of the synthetic homologue prostigmine, effects a prompt and striking restitution of muscular power in a few minutes, of a few hours' duration. If we assume that the basic difficulty is one of balance between liberation of acetylcholine and its destruction by choline esterase, it is easy to see that prostigmine, by inhibiting the latter reaction, will favor the maintenance of an effective level of acetylcholine for stimulation of muscular contraction. Thus the activity of prostigmine in this condition can be satisfactorily explained. Not explained, however, is whether the imbalance is due to deficient acetylcholine liberation or increased esterase activity. The fact that there cannot be demonstrated

in the muscle as a whole any increase in esterase activity does not necessarily mean that the esterase activity at the nerve endings is not pathologically increased, although there is a preponderance of evidence in favor of a deficiency of acetylcholine formation as the fundamental difficulty, or even a depression of muscular excitability by a curare-like substance. In support of this hypothesis, administration of stable choline esters, as carbaminoyl choline chloride and mecholyl, is effective in relieving the weakness of myasthenia, the action coming on slower but being more lasting than with prostigmine. Quinine has been shown to increase the weakness of patients with myasthenia; in fact, its use may be of diagnostic value. This is due probably to its known curare-like action, which depresses the activity of the muscle cells, and makes them even less liable to stimulation by the deficient concentration of acetylcholine present.

That there is a superabundance of acetylcholine present at the motor nerve endings in myotonia has not been demonstrated. However, the condition can be to a certain extent reproduced in muscle poisoned by physostigmine, and thereby sensitized to acetylcholine. Thus we would expect patients with myotonia to be made worse by the administration of prostigmine, and this is indeed the case. In this condition quinine is effective in bringing about some degree of improvement, by the same curare-like action which makes the myasthenia patient worse after quinine administration.

Thus we have two diseases, diametrically opposed in symptomatology, which respond in opposite manner to quinine and physostigmine, and thus present themselves as excellent biologic preparations for further work in elucidation of the mechanism of nervous transmission. As to the therapeutic possibilities, not so much can be said. The prolonged administration of quinine in large doses in the case of myotonia is effective in giving a considerable degree of relief of symptoms, although what its effect on the ultimate progress of the disease may be remains to be seen. Prostigmine is effective in myasthenia, dramatically if given parenterally. It must be frequently repeated, and there is evidence to suggest that over a prolonged period it loses its effect. It is the opinion of some⁶ that its use in no way influences the ultimate course, and may in fact accelerate it. By mouth, although less effective, it seems not to be harmful. The administration of stable choline esters merits further trial.

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Quantitative Studies of the Rate of Passage of Protein and Other Nitrogenous Substances Through the Walls of Growing and of Mature Mammalian Blood Capillaries. RICHARD G. ABELL (Laboratory of Anatomy, University of Pennsylvania). Information concerning the rate of passage of nitrogenous substances through the walls of growing blood capillaries was secured with "moat" chambers inserted in rabbit's ears. In such chambers the growing capillaries can be observed with the microscope, their condition recorded, and their area calculated. Nitrogenous substances, after having passed through the walls of these capillaries, diffuse into a moat, or reservoir, of known volume, from which they can be removed and analyzed quantitatively.

(1) Analyses were made of the total nitrogen that entered the moat during the first 24 hours following the introduction into the moat of a mammalian Ringer's solution. (2) The total surface of the capillaries involved was obtained from measurements of length and diameter. From these two sets of data the calculated amounts of total nitrogen that passed through per sq. mm. of endothelial surface per 24 hours were, in six different chambers, as follows: No. 1, 0.091 mg.; No. 2, 0.113 mg.; No. 3, 0.102 mg.; No. 4, 0.097 mg.; No. 5, 0.046 mg.; No. 6, 0.081 mg.

The slower rate of passage of these substances through the walls of the growing capillaries in Chamber No. 5 was associated with a slower rate of circulation in this chamber as observed directly with the microscope.

A part of the nitrogenous substances found within the moats of these chambers was protein. Assuming that this protein was not synthesized extravascularly, and using calculations similar to those described above, in the one chamber in which protein analyses have so far been made (Chamber No. 3), but basing the estimation on a collection period 48 hours in length, *protein* nitrogen came through at the rate of 0.039 mg. per sq. mm. of capillary surface per 24 hours. This compares with the figure for *total* nitrogen of 0.102 mg. Thus of the *total* nitrogen that came through the walls of the growing capillaries in this chamber per 24 hours, approximately $\frac{1}{3}$ was *protein* nitrogen.

The results secured with a new type of chamber, the "filter disc" chamber, indicate that protein accumulates less rapidly in the moat when the capillaries are mature than when they are growing.

Hypophysis in Protein Metabolism. K. E. PASCHKIS (Medical Research Laboratory, Samuel S. Fels Fund, Philadelphia). In previous experiments (with A. M. Schwoner) a method for testing regulation of protein metabolism was found. A gelatine test meal is followed by a marked rise in blood amino N. If a second gelatine test meal is given

3 hours after the first there is normally no second rise of blood amino N or only a very small rise. Cases of pituitary cachexia (Simmonds' disease) tested in this way showed a marked rise of blood amino N following the second gelatine test meal. One of the factors responsible for the normal regulation is the pituitary.

It is known that alkaline pituitary extracts containing growth hormone influence protein metabolism. We were able to confirm the findings of previous authors that such pituitary extracts produce a drop in blood urea N and blood amino N in rats, dogs or guinea pigs.

As we had found in our investigations with the double gelatine test meal that a factor of pituitary origin comes into action after a protein meal, we next attempted to trace this factor. Human individuals were put on a diet very rich in protein for 3 days and for 3 days on a carbohydrate-fat diet practically lacking protein. After protein feeding, urine and alcoholic urine extracts injected into rats led to a drop of urea N and amino N in the rats' blood. This effect was absent when urine after carbohydrate-fat diet was used for injection.

These results together with the results of previous experiments mentioned above make it very probable that the factor we have traced in the urine after protein feeding is the pituitary factor (hormone) active in protein metabolism. We have some reason to doubt whether this factor is identical with the growth hormone.

A further analysis seems to prove that this factor not only enhances anabolism of higher protein constituents from amino acids, but at the same time inhibits catabolism of amino acids and urea formation.

The Structure of the Mammalian Carotid Sinus and Adjacent Arteries. WILLIAM H. F. ADDISON (Department of Anatomy, University of Pennsylvania). The carotid sinus is the first part of the internal carotid artery, at the bifurcation of the common carotid artery into the external and internal carotid arteries. The structure of the sinus is characterized by the thinness of its walls, the presence of much elastic tissue and the lack of muscle in its tunica media. The transition region, where the elastic-walled sinus continues into the muscular internal carotid artery, is characterized by a sudden narrowing of the external diameter and of the lumen, and by an abrupt thickening of the vascular wall. This thickening is due chiefly to the appearance of great masses of smooth muscle, circularly arranged and replacing most of the elastic tissue. This arrangement of tissues in the carotid sinus has been seen in a number of mammals, including the opossum, deer, cat, dog, rhesus monkey, and a newborn child.

The structural arrangement seen in the wall of the carotid sinus is found at the beginning of neighboring arteries. The first branch of the external carotid artery in the dog is the occipital artery. The beginning of the occipital artery is somewhat dilated and its wall is composed chiefly of elastic tissue. From these similarities to the carotid sinus, the first part of the occipital artery might be termed the "occipital sinus." From the "occipital sinus" arises a branch, also elastic in structure, and from this branch comes the artery which supplies the carotid body. The artery to the carotid body is likewise elastic, non-muscular in structure. In each of these arteries the elastic tissue in the

middle coat is replaced by smooth muscle as soon as it has given off its elastic walled branch. There is thus a little system of arteries in the locality of the carotid sinus which have elastic walls, similar to those of the carotid sinus.

Experimental Hypertension in Nephrectomized Parabolic Rats. WILLIAM A. JEFFERS, M. AUGUST LINDAUER, PAUL H. TWADDLE, and CHARLES C. WOLFERTH (Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, and the Morris W. Stroud, Jr. Fellowship in Cardiology of the Pennsylvania Hospital). Litter-mate male rats were joined in parabiosis when they were 20 to 30 days old. Successive nephrectomies were performed until only one kidney remained to function for both animals.

Nineteen pairs of rats so prepared were observed daily with particular reference to changes in blood pressure. In the last 4 days of their lives the totally nephrectomized rats showed a significantly preponderant incidence of hypertension, as compared with their mates having one kidney. During the same period of survival, only the totally nephrectomized animals also developed increasing azotemia and weight loss.

In a second series of 11 pairs, the totally nephrectomized animals all showed a larger blood volume than the rats retaining one kidney. It is suggested that the hypertension occurring late in the survival period of totally nephrectomized rats living in parabiosis is due primarily to an increase in blood volume.

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